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TREATMENT OF POSTARSPHENAMINE DERMATITIS

LOREN W. SHAFFER, M.D.
DETROIT

Numerous and diverse hypotheses have been offered to explain the mechanism involved in the production of arsphenamine dermatitis. The more intensively one reviews the literature the more confused the problem becomes. It is impossible, therefore, to give a satisfactory short summary as an introduction to this paper. Excellent reviews of such theories have been given recently by Franklin,[1] Bernstein,[2] Stokes,[3] Raiziss[4] and many others. A few of the outstanding theories should be mentioned, however, because of the causal suggestions they offer in the field of therapy.

According to Moore and his co-workers,[5] it is now generally believed that postarsphenamine dermatitis is the result of direct sensitization to arsphenamine, to the products of its metabolism or to a state of general allergic instability or to a hypersensitiveness not necessarily absolutely specific for arsphenamine. This theory has been materially strengthened by experimentation on animals and the clinical observations of Frei,[6] Nathan and Munk,[7] Sulzberger and his co-workers,[8] Moore,[5] Schoch,[9] Bernstein[2] and others. Arsphenamine dermatitis cannot, however, be

Read at the Fifty-Sixth Annual Meeting of the American Dermatological Association, Chicago, June 9, 1933.

1. Franklin, J. L.: Salvarsan Dermatitis, Brit. J. Dermat. **42**:165 (April) 1930.

2. Bernstein, F.: Pathogenesis of Chronic Salvarsan Dermatitis, Arch. f. Dermat. u. Syph. **165**:397, 1932.

3. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company 1928, p. 330.

4. Raiziss, G. W., and Koppelman, A.: Reactions Following the Administration of Arsphenamine and Its Derivatives, J. Chemotherapy **4**:7 (April); 55 (July) 1928.

5. Moore, J. E.; Woo, S. T. T.; Robinson, H. M., and Gay, L. N.: Reactions of the Skin Following the Intradermal Injection of Arsphenamine, Arch. Dermat. & Syph. **23**:74 (Jan.) 1931.

6. Frei, W.: Sensitization of the Skin with Neosalvarsan, Klin. Wchnschr. **7**:539 (March 18) 1928.

7. Nathan, E, and Munk, A.: Experimental Sensitization and Allergy of the Skin to Salvarsan, Klin. Wchnschr. **8**:1354 (July 16) 1929.

8. Chargin, L.; Sulzberger, M. B., and Crowley, D. F.: The Hypersensitiveness of the Skin to Arsphenamine as Determined by the Contact Test, Arch. Dermat. & Syph. **22**:237 (Aug.) 1930.

9. Schoch, A. G.: Patch Test and Element of Syringe Contamination in Arsphenamine Sensitization Dermatitis, J. A. M. A. **98**:1367 (April 16) 1932.

placed without qualification in the group of dermatoses which can be explained entirely on the basis of acquired hypersensitiveness. The discovery of such sensitivity in advance of the onset of dermatitis by intradermal, scratch or patch tests has failed, although, according to Schoch,[9] they may be used to determine whether a patient may continue a particular type of arsphenamine treatment after an attack of dermatitis. The question as to whether the sensitization is specific for the arsphenamine as such or to its arsenic or phenolic factors remains to be determined. Cases of sensitization produced by intradermal or scratch tests have caused the patch method of testing to be recommended as the one of choice. The possibility of producing sensitization by accidental paravenous injection has received much discussion. Since subcutaneous injections fail to sensitize animals, I feel that small amounts of arsphenamine accidentally deposited intradermally while the needle is being withdrawn on completion of the injection may at times induce sensitization, rather than that such sensitization is dependent on gross paravenous infiltrates.

The hepatotoxic and the epidermovasculotoxic theories have many advocates. The hepatotoxic explanation accounts for cutaneous reactions on the theory that the liver is damaged by the drug and becomes incapable of detoxicating the arsphenamine when it is subsequently introduced, or else causes a perverted metabolism of the arsphenamine. The occurrence of jaundice coincident with dermatitis is not rare. Numerous methods of testing the function of the liver have been suggested, particularly in the German literature, none of which is entirely satisfactory. Recent reports of the use of liver extract in the treatment of arsenical dermatitis, with excellent results, as well as the use of sodium dehydrocholate [10] in the prevention of hepatic reactions or postarsphenamine jaundice, are seemingly further proof of such association.

The epidermovasculotoxic or vasoneurotic theory is admitted by the allergists as a part of the mechanism for the production of arsphenamine dermatitis. Myers and his co-workers [11] published several excellent papers in which, on a basis of detailed chemical and blood studies, they amplified the theories of Milian and Widal, stressing a primary toxic effect on the involuntary or autonomic nervous system which causes excessive loading of arsenic in the skin and liver and produces damage that might lead to dermatitis or jaundice. The chief point of attack is the circulatory system, particularly the walls of the blood vessels. The most important symptoms can be referred to relaxation of the capillary

10. Appel, B.: Sodium Dehydrocholate in Arsphenamine Poisoning, Arch. Dermat. & Syph. **27**:401 (March) 1933.

11. Rosen, I.; Müller, E. F., and Myers, C. N.: Studies on the Complex Nitritoid Crisis after the Intravenous Administration of Arsenicals, Arch. Dermat. & Syph. **10**:316 (Sept.) 1924.

endothelium. The angioneurotic phenomena of the nitritoid crisis are inseparably associated with the vasculotoxic theory. For this reason a discussion of the prevention of postarsphenamine dermatitis should include the prophylaxis of the nitritoid crisis.

The accumulated evidence pointing to the possibility of arsphenamine stirring up some latent infection in the patient's body cannot be overlooked. Glaser [12] and others reported cases in which latent malaria had been brought into activity by arsphenamine, although Fischer [13] showed that this might be brought about by any severe disturbance in the body. Loeb [14] reported cases of encephalitis stimulated by arsphenamine. Stokes and his collaborators [15] reported an epidemic of postarsenical jaundice, and advanced their theory of intercurrent or focal infection.[16] Milian [17] stated that many mysterious postarsphenamine reactions are due, as a class, to biotropism of the drug for some unknown micro-organisms, such as those causing roseola, rubella, lichen planus, herpes zoster or infectious erythema. Most cases of "ninth day erythema [18]" are examples of this pathogenesis. This type of eruption is not commonly recognized, and is usually thought to be the start of an exfoliative dermatitis. It appears nine days after the first injection of arsphenamine and usually assumes the form of scarlatina or rubella. There is a history of a previous clinical attack of the disease in question, and, although the attack is mild, the symptoms, including fever, are typical. On recovery these patients are not sensitive to further arsphenamine therapy.

A discussion of the toxic effects of arsphenamine would not be complete without some consideration of the reticulo-endothelial system. The control of immunity through this system and the chemotherapy of syphillis are receiving much attention in the foreign literature. It is probable that many of our prophylactic and therapeutic measures used in combating the toxic effects of arsphenamine have their seat of action

12. Glaser, F.: The Rousing of Malaria by Arsphenamine, Med. Klinik **17**:867 (July 17) 1921.

13. Fischer, C.: The Provocative Effect of Salvarsan in Chronic Malaria, Dermat. Wchnschr. **73**:826, 1921.

14. Loeb, H.: Salvarsan Death and Influenza, Arch. f. Dermat. u. Syph. **138**:252 (May) 1921.

15. Stokes, J. H.; Ruedeman, R., Jr., and Lemon, W. S.: Epidemic Infectious Jaundice and Its Relation to the Therapy of Syphilis, Arch. Int. Med. **26**:521 (Nov.) 1920.

16. Stokes, J. H., and Cathcart, E. P.: Contributory Factors in Postarsphenamine Dermatitis, Arch. Dermat. & Syph. **7**:14 (Jan.) 1923.

17. Milian, G.: The Rousing of Latent Malaria with Neoarsphenamine, Ann. d. mal. vén. **17**:1 (Jan.) 1922.

18. Gjessing, H. C.: Form of Salvarsan Dermatitis (Ninth Day Erythema) in Which Salvarsan Treatment Is Continued, Acta dermat.-venereol. **9**:185 (Oct.) 1928.

in protecting or allaying the cells of this system. The reticulo-endothelial system (especially prominent in the spleen, lungs, bone marrow, Kupffer's cells of the liver and the cutaneous connective tissue) through its property of phagocytosis is an important agent in the purifying mechanism of the blood. It is also generally considered to be the chief source of antibody production. The system is considered to be of great importance in intravenous therapy, for many materials (including arsphenamine) injected into the blood stream disappear from it quickly, with deposition in the reticulo-endothelial cells.

In line with the allergic hypothesis of arsenical dermatitis, Bohm and Vamos [19] attempted to determine experimentally the mechanism of esophylaxis. They concluded that the reticulo-endothelial system is the source of the immune substances in this phenomenon, and that the function is stimulated by substances produced by the destructive action of certain irritants on the cells of the skin. The connection between the skin and the reticulo-endothelial system is probably through the blood stream rather than through the autonomic nervous system. Levina [20] stated the belief that the reticulo-endothelial system is a bilirubin-producing apparatus. Marked bilirubinemia indicates hyperfunction of the reticulo-endothelial system and hypofunction of the liver, caused by the toxic action of either the syphilitic virus or the arsphenamine. The reticulo-endothelial system plays an enormous rôle in the struggle against syphilitic infection, and the arsphenamine reactions as a group are largely referable to centers for localization of the reticulo-endothelial system in the liver, the suprarenal glands, the bone marrow, the capillary endothelium and the skin. Measures aimed at the protection of this system are, therefore, important in the prevention of reactions to arsphenamine.

TREATMENT OF THE NITRITOID CRISIS

Theories as to the etiology of the nitritoid crisis are nearly as numerous as those for the etiology of arsphenamine dermatitis. They may be divided mainly into two theories: the physicochemical theory, which assumes a primary colloid change evidenced by albuminous precipitates or erythrocytic agglutination, and the theory of a disturbed sympathetic-vagus equilibrium, which assumes an abnormal hypersusceptibility of the parasympathetic nervous system in the angioneurotic symptom complex. The prevention of the nitritoid crisis follows closely such ideas on etiology and may be taken as proof of the soundness of such theories.

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19. Bohm, A., and Vamos, L.: Esophylaxis and the Reticulo-Endothelial System, Dermat. Ztschr. **62**:246 (Nov.) 1931.

20. Levina, B.: The Reticulo-Endothelial System and Syphilis, Sovet. vestnik venerol. i dermat. **9**:690 (Nov.-Dec.) 1931; abstr. Arch. Dermat. & Syph. **26**:517 (Sept.) 1932.

The physicochemical methods of treatment, according to Milbrandt,[21] depend on an increase in the colloid stability of the blood serum and of the fluids injected. This may be secured by alkalis which call forth a decreased surface tension, by an increase in viscosity as induced by dextrose, by the protective colloid effect of hydrophilic colloids such as blood serum and gelatin and, finally, by dehydration occasioned by hypertonic solutions.

Substances which paralyze the vagus nerve such as atropine or substances which stimulate the sympathetic system such as epinephrine, ephedrine and calcium have had wide use. The substances that particularly increase tolerance for arsphenamine influence the vascular system either peripherally or centrally, either directly or indirectly. The indications are to protect the vascular system and increase the stability of the plasma. This may be secured by dextrose or saline solution, as has been shown by Myers and Mueller,[22] or by brain hypnotics such as magnesium sulphate or a dialysate of valerian, as recommended by Spiethoff and Wiesenack.[23] According to Milbrandt, such hypnotics offer greater protection against arsphenamine shock than any other measures commonly employed. Such use of hypnotics has had, I believe, little recognition in this country.

THE PREVENTION OF ARSPHENAMINE DERMATITIS

The trite saying that "an ounce of prevention is worth a pound of cure," has no better application than to arsphenamine dermatitis. Most cases of frank arsphenamine dermatitis present warning signs before the generalized dermatitis begins. If these warning signs are looked for or inquired about, the dermatitis can probably be stopped before it gets a start. This phase of prevention was well covered by Stokes[24] in his "decalogue of dermatitis prevention." Cases of dermatitis exfoliativa are rare in large, well organized services for the treatment of syphilis, and most cases are fed to our city hospitals by the practitioners who treat syphilis only occasionally or who do not recognize the importance of such warning signs.

These early prodromal cases offer a different problem than those showing frank exfoliative dermatitis. In most early cases treatment with arsphenamine can be guardedly continued by changing to a

21. Milbrandt, W.: Etiology and Therapy of the Nitritoid Crisis and Arsenical Dermatitis, München. med. Wchnschr. **78**:1860 (Oct. 30) 1931.

22. Myers, C. N., and Mueller, E. F.: Antagonistic Action of Carbohydrates and Electrolytes on Behavior of Leucocytes and Excretion of Arsenic Following Administration of Arsphenamines, Am. J. Syph. **12**:157 (April) 1928.

23. Spiethoff and Wiesenack, quoted by Milbrandt.[21]

24. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1928, p. 337.

different type of arsenical, small doses, etc., until further sensitivity is determined. It is probable that a true allergic state does not develop if these early cases are stopped before the skin is damaged by the dermatitis to the extent of permitting arsenic to be deposited, or at least to act as a fulminator to severe involvement.

The addition of various substances to the arsphenamine to render it less toxic would be well suited to this type of case. Physiologic solution of sodium chloride, dextrose, gelatin, sodium thiosulphate and calcium have all been recommended for this purpose.[25] Further clinical observations and studies should be made. Dextrose and sodium thiosulphate especially, for reasons to be stated, should receive consideration.

Another preventive measure of which there is little definite knowledge is diet. Lake [26] showed that the presence of carbohydrates in rats materially increased the tolerance to arsphenamine, which observation required standardization of the diets of the rats used in toxicologic tests on arsphenamine. In some clinics [22] the patients receive 2 or 3 tablespoonfuls of dextrose from one-half to two hours before treatment, and it is thought to reduce reactions materially. On the other hand, Craven [27] stated that a diet high in fat and in protein provides the maximum protection against injury to the liver from arsphenamine, while diets high in carbohydrate increase the susceptibility.

SODIUM THIOSULPHATE

Sodium thiosulphate has until recently been the only popular detoxicating agent used as an adjunct to the commonly employed methods of treatment. Clinical experience has proved that sodium thiosulphate is a valuable detoxicating agent for heavy metals, for arsenic in particular, but just how this action is brought about is not known. According to Kahn and Loevenhart [28] and Young,[29] it decreases the rate of arsenic excretion. It transforms the arsenic into a less toxic, less therapeutically efficient and a less easily excretable product. On the other hand, accord-

25. Lipskeroff, I. B., and Grebin, Z. N.: Comparative Value of Methods to Reduce Harmful Effects of Neoarsphenamine by Different Vehicles, Arch. Dermat. & Syph. **16**:442 (Oct.) 1927.

26. Lake, G. C.: Certain Factors Connected with Toxicological Testing of Arsphenamine, Am. J. Syphilis **5**:96 (Jan.) 1921.

27. Craven, E. B.: Importance of Diet in Preventing Acute Yellow Atrophy During Arsphenamine Treatment, Bull. Johns Hopkins Hosp. **48**:131 (March) 1931.

28. Kahn, H., and Loevenhart, A. S.: The Antagonism Between Sodium Thiosulphate and Arsenical Compounds, J. Pharmacol. & Exper. Therap. **27**:160 (March) 1925.

29. Young, G. A.: Effect of Sodium Thiosulphate on Arsenic Elimination, J. Pharmacol. & Exper. Therap. **31**:217 (July) 1927.

ing to Myers,[30] it increases the arsenic excretion. He believes that its action is through the presence of the sulphydryl group, which is able to change insoluble arsenic compounds developed in the skin into soluble ones, if given early in the course of dermatitis. According to Kabilek,[31] sodium thiosulphate desensitizes and is of value in all allergic states (serum sickness, eczema, urticaria). He believes that sodium thiosulphate circulates in the blood as a neutral salt and does not decompose until it reaches a diseased area which has a higher acidity and temperature.

Hubschman,[32] Lewin [33] and Voegtlin and Dyer [34] recommended combining sodium thiosulphate with neoarsphenamine in order to reduce reactions and to avoid arsenical complications. They stated that such solutions are not more toxic than neoarsphenamine alone, that they give equal if not better clinical results, and that the tolerance of the patient is increased. Sodium thiosulphate increases diuresis, acts primarily on the reticulo-endothelial system and has, without question, distinct pharmacologic action.[35]

Sodium thiosulphate, hailed as a specific in the treatment of arsphenamine dermatitis after its introduction by McBride and Dennie,[36] affords an occasional spectacular result, and has undoubtedly reduced mortality and the length of hospitalization; but it is nevertheless in many cases extremely disappointing. Its value lies in its use early in the disease. After damage from arsenic has taken place thiosulphate in any amount will fail to hasten the resolution of the arsphenamine dermatitis.[37] Sodium thiosulphate should therefore be given at the earliest possible moment. I would recommend that 1 Gm. of the freshly prepared solution be given intravenously at daily intervals for from three to six doses. A smaller dosage at the start is in line with the view that large doses

30. Müller, E. F.; Metz, G. P., and Myers, C. N.: Arsenic Lesions of the Skin, Arch. Dermat. & Syph. **15**:186 (Feb.) 1927.

31. Kabilek, J.: Thiosulphate Therapy, Česká dermat. **9**:507, 1928.

32. Hubschman, K.: Employment of Mixtures of Neosalvarsan and Sodium Thiosulphate in the Therapy of Syphilis, Urol. & Cutan. Rev. **34**:91 (Feb.) 1930.

33. Lewin, E. M.: Use of Sodium Thiosulphate in Dermatitis and Hepatic Dysfunction Following Arsphenamine Injections. Dermat. Wchnschr. **86**: 32 (June 23) 1928.

34. Voegtlin, C., and Dyer: Arsphenamine-Sodium Thiosulphate Treatment of Experimental Syphilis, Pub. Health Rep. **42**:1045 (April 15) 1927.

35. Myers, C. N.: Personal communication to the author.

36. McBride, W. L., and Dennie, C. C.: Treatment of Arsphenamine Dermatitis and Certain Other Metallic Poisonings, Arch. Dermat. & Syph. **1**:651 (June) 1920.

37. Osborne, E. D.; Putnam, E. D., and Hitchcock, B. S.: Effect of Arsenic on Rabbits, Arch. Dermat. & Syph. **25**:419 (March) 1932. Osborne, E. D.: ibid. p. 438.

would cause too rapid elimination, or freeing of arsenic from the tissues with subsequent exacerbation of symptoms. It would seem that delay in securing effective thiosulphate dosage would outweigh the possibility of such exacerbation. Sodium thiosulphate has a tendency to produce alkalosis, so that it should not be continued indefinitely.

LIVER THERAPY

Recent articles by Spiethoff,[38] Pinard and Corbillion[39] and Milbrandt[21] announced surprisingly good results in the treatment of postarsphenamine dermatitis from injections of liver extracts. Spiethoff stated that the influence of treatment with liver in severe cases of arsphenamine dermatitis was soon apparent in definitely improved spirits, general bodily condition and appetite, a lower temperature and improvement in the condition of the skin. In experimental animals with severe intoxication from arsphenamine, with great emaciation and even prostration, great improvement followed injections of liver extract in from one to two hours. In man, he stated, intramuscular injections of liver extract were painless and were given three times weekly in doses of from 5 to 10 cc. Liver extract may also be given by mouth. Spiethoff stated that in cases of mild dermatitis, treatment with arsphenamine could be continued in conjunction with liver extract without disturbance of the skin, and that bismuth dermatitis is similarly improved. Milbrandt confirmed the prompt success of liver therapy. He claimed that since such therapy stimulates the disturbed function of the liver, cures chronic arsphenamine intoxication and works prophylactically and therapeutically on the manifestations of arsphenamine sensitization, it is further evidence of insufficiency of the liver as a cause of arsphenamine dermatitis.

CALCIUM THERAPY

The use of calcium in arsphenamine therapy goes back to Spiethoff and Wiesenack,[40] who emphasized both the prophylactic and the therapeutic usefulness of calcium. Gerwig,[41] in a detailed article on "Calcium Therapy in Dermato-Syphilology," recommended giving neoarsphen-

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38. Spiethoff, B.: Therapeutic Use of Hepatrat (Liver Extract) in Dermatitis, München. med. Wchnschr. **76**:577 (April 5) 1929; The Value of Parenteral Liver Therapy, München. med. Wchnschr. **78**:1009 (June 12) 1931.

39. Pinard, M., and Corbillion: Rapid Improvement of Arsenical Erythroderma after Large Injections of Liver Extract, Bull. Soc. franç. de dermat. et syph. **38**:32 (Jan.) 1931.

40. Spiethoff, B., and Wiesenack, H.: Clinical and Pharmacologic Observations on Intravenous Administration of a Calcium Preparation (Afenil), Deutsche med. Wchnschr. **46**:1219 (Oct. 28) 1920.

41. Gerwig, A.: Calcium Therapy in Dermato-Syphilology, Dermat. Wchnschr. **91**:1090 (July 26) 1930.

amine dissolved in 10 cc. of a 10 per cent solution of calcium gluconate as a preventive of nitritoid crises, delayed fever, malaise and vomiting and especially in cases complicated by active tuberculosis. Schamberg and Brown,[42] in their studies on calcium metabolism, showed that calcium leaves the blood stream very rapidly and that a lower but more sustained curve of blood calcium may be secured by either oral or intramuscular administration. This would confirm the German principle of saturation or supersaturation by intense calcium therapy. Karrenberg,[43] Herxheimer and Herrmann,[44] Gerwig [45] and others recommended this saturation dosage in the treatment of arsphenamine dermatitis and reported excellent results from its use. As an example of such supersaturation, Gerwig [41] recommended three injections intravenously daily of 10 cc. of a 10 per cent calcium gluconate solution, three injections daily of the same amount intramuscularly and two tablespoonfuls of the powder in water by mouth three times daily for three days, after which treatment with calcium may be continued by mouth alone. A more conservative dosage calls for 10 cc. intravenously, 10 cc. intramuscularly and from 1 to 2 tablespoonfuls three times daily by mouth. Such calcium therapy as I am acquainted with in this country does not approach this in intensity, which may explain the lack of success and enthusiasm in its use in arsphenamine dermatitis.

DEXTROSE

The literature on the use of dextrose in the treatment of many varied conditions is voluminous. Its greatest field of usefulness has been in the treatment of hepatitis and myocarditis. It has thus been shown that the administration of large amounts of dextrose decreases the harmful effects of many substances (including arsphenamine) on the liver. A liver poor in glycogen is exposed to much more damage than a liver whose cells are laden with rich reserves of glycogen. Cross and Blackford [46] reported a case in which death caused by hypoglycemia of hepatic origin followed the use of neoarsphenamine. The patient also had a mild exfoliative dermatitis. Intravenous administration of a

42. Schamberg, J. F., and Brown, H.: Some Studies of Calcium Metabolism; Discussion of a New Therapeutic Compound, Cong. Internat. de Dermat et de Syph., Copenhagen, 1930.

43. Karrenberg, C. L.: The Therapeutic Use of Calcium Gluconate in Dermatology, Dermat. Wchnschr. **86**:540 (April 21) 1928.

44. Herxheimer, K., and Herrmann, F.: Treatment of the Toxic Effects of Salvarsan, Fortschr. d. Therap. **6**:374 (June 25) 1930.

45. Gerwig, A.: Treatment of Arsphenamine Dermatitis, München. med. Wchnschr. **77**:1403 (Aug.) 1930.

46. Cross, J. B., and Blackford, L. M.: Fatal Hepatogenic Hypoglycemia Following Neoarsphenamine, J. A. M. A. **94**:1739 (May 31) 1930.

hypertonic solution of dextrose influences the osmosis in such a way that there is an exudation from the tissues into the blood. Pathologic substances (including arsenic) are removed from the cells and carried away by the increase in diuresis resulting from the hydremia or are metabolized and excreted by the protected and stimulated liver. Another beneficial action is a sort of activation of the protoplasm (Apel [47]) which can be recognized by the increase in the number and phagocytic activity of the leukocytes. This is definite evidence of a stimulating effect on the reticulo-endothelial system with its protective effect on the whole organism.

The dehydration of the body caused by a hypertonic solution of dextrose is probably one direct reason for its value in the treatment of any edematous or exudative dermatitis. Ernst [48] showed that a concentrated solution of dextrose (from 40 to 60 per cent) has a greater dehydrating effect than a solution of sodium chloride of the same osmotic pressure (about 10 per cent). This accounts for its value in any acute condition associated with increased cerebral pressure and would suggest its use in postarsenical acute hemorrhagic encephalitis. Apel [47] reported excellent results from the use of a hypertonic solution of dextrose injected intravenously in the treatment of eczema and dermatitis for it often brought relief from itching, exudation and inflammation in an astoundingly short time.

The use of dextrose in more dilute solutions (from 2 to 10 per cent) as a diluent for arsphenamine has been recommended by several investigators to prevent arsphenamine reaction, as well as its use by mouth preceding the injection. Arsenic combines with dextrose to form glucosides which are less toxic, which have a tendency to remain in the blood stream over a longer period and which are excreted more rapidly.[22] The question as to whether therapeutic efficiency is also reduced remains to be decided. It would therefore seem advisable for the present to limit such use of dextrose to cases that were proving reactive to treatment with arsphenamine.

CLINICAL EXPERIENCES IN THE TREATMENT OF ARSENICAL DERMATITIS WITH DEXTROSE

The staff [49] of the City Hospital in Detroit has employed dextrose occasionally in the treatment of postarsphenamine dermatitis for the past five years. It is difficult to evaluate the results, because the number of

47. Apel, C.: Skin Therapy with Calcarose, Dermat. Wchnschr. **91**:1344 (Sept. 6) 1930.

48. Ernst, M.: Experimental and Clinical Basis for the Use of Hypertonic Solution of Glucose, Deutsche Ztschr. f. Chir. **226**:222, 1930.

49. The dermatologic staff includes Drs. R. C. Jamieson, George VanRhee, H. L. Keim, A. Kirschner, C. K. Valade and Loren W. Shaffer.

patients treated was not large, and because cases of arsenical dermatitis vary greatly in the severity of manifestations and in the length of hospitalization. Spectacular results can at times be ascribed to any method of treatment. Results from the use of dextrose were encouraging, and at times almost miraculous, so that such treatment has been

Summary of Treatment and Results

Case	Duration of Dermatitis	Previous Arsphenamine Injections	Sodium Thiosulphate	Dextrose	Days in Hospital	Comment	Average Days in Hospital	
1	?	?	None.....	None.....	24	Recurred after six weeks		
2	1 week	22	2 inj.; 0.5 and 0.75 Gm.	None.....	26	Small amount of thiosulphate, and by mouth	27	
3	5 days	6	3 inj.; 0.5, 0.75 Gm. followed by oral medication	None.....	29			
4	3 weeks	8	Same as case 3	None.....	28			
5	2 days	2	3 inj.; 0.5 Gm. each	None.....	6	Questionable cases "ninth day erythema"	6	24
6	9 days	1	Same as case 5	None.....	6			
7	2 weeks	4	14 inj.; total 13.5 Gm.	None.....	31	Moderate to intense thiosulphate therapy	33	
8	1 week	16	8 inj.; 2-3 day intervals; total 7.0 Gm.	None.....	25			
9	?	?	Daily inj. 1.0 Gm. for 35 days; total 35.0 Gm.; also 1 Gm. by mouth t. i. d.	None.....	43			
10	5 weeks	6	None.....	50, 50, 50, 50 and 15 cc. 50% sol. intravenously daily	7	Surprisingly rapid response to small amounts of dextrose 50% sol.	8	
11	3 weeks	6	1 inj; 0.5 Gm.	3 inj.; 50 cc. 50% sol.	5			
12	4 days	4	2 inj.; 0.5 and 1.0 Gm.	2 inj.; 50 cc. 50% sol.	4			
13	3 weeks	12	3 inj.; 0.5 Gm. alt. days	50, 75, 75, 75 cc. 50% sol. on alternate days	13			
14	2 weeks	7	4 inj.; 0.5 Gm. alt. days	25, 25, 25 cc. 50% sol. on alt. days	12 (death)	Acute cardiac decompensation		13
15	10 days	7	0.5, 0.75 and 1.0 Gm. daily 6 days; total 5.0 Gm.	1st day 1,000 cc. 5% sol. 2d day 3,000 cc. 5% sol. 3d day 2,000 cc. 5% sol. 4th day 1,600 cc. 5% sol.	31	5% solution of dextrose in massive doses	31	

continued. The usual supportive and local measures of treatment were employed. More patients with arsenical dermatitis than those represented in the table were treated, both with and without dextrose during the five year period surveyed, but the records could not be located in the hospital files. For convenience in comparing results, the patients are grouped into those receiving thiosulphate alone and those receiving dextrose alone or in combination with thiosulphate.

COMMENT

It will be noticed in the cases in which sodium thiosulphate was employed alone that the duration of hospitalization was remarkably uniform, except for case 5, in which the dermatitis appeared after the second injection of neoarsphenamine and in which treatment was begun within two days after its appearance. In case 6, in which the dermatitis appeared after the first injection of neoarsphenamine a diagnosis of arsenical dermatitis was questionable. Either or both of these cases may have been examples of the infectious type or "ninth day erythema" of the French. The average length of hospitalization was twenty-four days. In the case in which neither thiosulphate nor dextrose was given a recurrence was recorded. Intensive and long-continued thiosulphate therapy, as represented by cases 7 and 9, did not reduce the duration of hospitalization (average, thirty-seven days), which is in line with the reference already made to the futility of such a procedure.

The number of patients treated with a hypertonic solution of dextrose, as represented by this report, is small, but they confirm the impression of the almost miraculous effects of this therapy at times, especially in the acute edematous and exudative stages of arsphenamine dermatitis. The action of the solution is probably largely a dehydrating effect on the tissues. The difficulty of giving intravenous treatment in this stage of the disease and the tendency of concentrated dextrose to produce thrombosis of the vein in which the injection is made are decided objections to this method of treatment. To obviate the possibility of thrombosis, large amounts (in this case, heroic) of a dilute solution of dextrose were tried, as in case 15. Seemingly the purpose of dehydration was defeated by such large amounts of fluid; therefore the experiment failed. Very slow injection would probably obviate the tendency to thrombosis. The occasional occurrence of chills after the intravenous administration of dextrose demands the highest purity of dextrose and distilled water to combat the "pyrogenic" effect that is such a problem in the use of prepared solutions of dextrose. An average hospitalization of eight days in the first four cases, in which a 50 per cent solution of dextrose was administered intravenously, is much better than could be expected for a more diversified large group. In case 14, the only one in which death occurred, it was not felt that treatment had anything to do with the fatality, since dextrose is accepted as a valuable supportative measure in myocardial conditions. The patient was a youth of 20 with a chancre of ten days' duration when antisyphilitic treatment was begun. He died of acute decompensation owing to insufficiency of the mitral valve, probably precipitated by the dermatitis.

The possibility of administering dextrose orally has been considered. It is readily absorbed, and such a method would obviate the objections to its intravenous administration. The rapid dehydration produced by an intravenous injection of a 50 per cent solution of dextrose would not be secured, and perhaps therefore the results would be less satisfactory. Dempster [50] and others recommended oral administration for those general conditions for which dextrose therapy is indicated.

One pound of commercial glucose is added to 1 quart of water and the juice of two lemons, and the solution is boiled for five minutes. Its use in this manner, prior to the administration of arsphenamine, might reduce the incidence of complications as suggested under diet in the prevention of reactions. It might also afford a valuable addition to other recommended methods of treatment of arsenical poisoning and dermatitis, such as saturation of the tissue with calcium or liver therapy.

The possibility of the production of acidosis by intensive dextrose therapy must be considered. The blood sugar in uncomplicated cases of arsphenamine dermatitis is apparently within normal limits. The values of blood sugar in eight of the reported cases (rest not taken) were within normal limits. Unfortunately, no determinations were made for acidosis during dextrose therapy. It is obvious that such therapy should not be used in even a very mild case of diabetes. It would probably be a better procedure to give 5 units of insulin one-half hour after the administration of dextrose, as suggested by Holtz.[51]

It is evident that much more can be done for postarsphenamine dermatitis than to limit one's efforts to the use of sodium thiosulphate alone. The introduction of calcium thiosulphate was a step in this direction, but the amount of calcium so administered falls far short of that required for the saturation methods reviewed. If used to satisfy the requirements for thiosulphate it should be fortified by calcium therapy. (I have had no experience with liver or calcium saturation therapy.) Fortunately, cases of arsphenamine dermatitis are rare. To present opportunities for investigating and comparing the clinical response with dextrose, calcium or liver therapy, and various combinations, in addition to the early use of thiosulphate, is not feasible for any one syphilologic center. Parts of the problem might be assigned to different investigators. I propose to treat any new patient (nondiabetic) having accessible veins with 1 Gm. of sodium thiosulphate and 50 cc. of a 50 per cent solution of dextrose injected intravenously daily for from three to five days. The administration of the dextrose should be followed in one-half hour by

50. Dempster, J. H.: Oral Administration of Glucose, J. Michigan M. Soc. **26**:304 (May) 1927.

51. Holtz, F.: Scientific Basis and Indications for the Use of Glucose in Therapy, München. med. Wchnschr. **79**:1189 (July 22) 1932.

the five units of insulin. Patients in whom venipuncture is difficult or impossible are to be treated with liver extract by intramuscular injection or with calcium gluconate according to the saturation technic of Karrenberg.[43]

C. N. Myers, Ph.D; and G. W. Raiziss, Ph.D., supplied abstracts, particularly with reference to the reticulo-endothelial system.

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DISCUSSION

Dr. John H. Stokes, Philadelphia: Striking advances in the medical management of arsphenamine dermatitis have been made in recent years, to which Dr. Shaffer calls attention in a most timely way. The American medical profession can well afford to extend its practice to these innovations in the use of dextrose, insulin and liver therapy. In a recent case they were life-saving after the commonly used procedures, including sodium thiosulphate, had failed. My impressions coincide with Dr. Shaffer's on the undesirability of the prolonged use of sodium thiosulphate for patients with exfoliative dermatitis. Its best work is done, I believe, in the first three or four injections. Some of the remarkable results attributed to any method of treatment for cutaneous reactions due to arsphenamine may be ascribed to the spontaneous recoveries of the nine-day erythema type of reaction as, again, Dr. Shaffer points out.

Dr. Charles C. Dennie, Kansas City: Dr. McBride and I have been interested for many years in arsphenamine dermatitis. The use of dextrose is no new thing to us. We have used it for a long time in the treatment of the condition. One of our patients became unconscious and remained so for several days; dextrose in that case was the treatment that relieved the condition.

Another method that should be mentioned is the withdrawal of blood and the transfusion from a proper donor of new blood. I am satisfied that some of our patients have been saved by this treatment. Some years ago we mentioned the association of the liver and the skin in arsphenamine dermatitis; we also mentioned the fact that in some cases of arsphenamine dermatitis that were not bad in the beginning the use of sodium thiosulphate produced a marked edema. After investigation we felt that this condition was due to the retention of the sodium chloride in the tissues. We believe that in most cases of severe arsphenamine dermatitis there is edema, and that in those cases in which edema does not develop the condition is not arsphenamine dermatitis.

Dr. Samuel Ayers, Jr., Los Angeles: I am very much indebted to Dr. Shaffer for some new ideas relative to the treatment of arsphenamine dermatitis, but I take exception to the statement that long-continued use of sodium thiosulphate is dangerous. I have been particularly interested in finding a number of cases of arsenical dermatitis of undetermined origin. The presence of arsenic in the urine in pathologic amounts has substantiated the diagnosis. The administration of sodium thiosulphate over a period of weeks or months has been responsible for the gradual disappearance of the arsenic from the urine, and for the gradual clinical cure. I have treated patients with sodium thiosulphate for four or five months or more, with no bad results, and I considered the patients cured. One man had been bedfast for weeks.

The output of phenolsulphonphthalein was down to 5 per cent. There were atrophy of the interosseous muscles, a large amount of arsenic in the urine, a

generalized exfoliative dermatitis, edema and loss of hair. This patient was treated with sodium thiosulphate for over a year. Temporarily there was an increase of symptoms, especially of the edema and ascites, which I think was due to the release of arsenic which had been stored in the tissues and to the subsequent flooding of the system. This person recovered, so far as the dermatitis was concerned. The renal function rose to about 16 per cent, but he died a year and a half later of cardiorenal complications. I think that the dehydration treatment is of particular value in cases of arsenical poisoning showing cerebral edema. Perhaps sodium thiosulphate plus dextrose may cure these patients. I think that giving sodium thiosulphate for a few days only is no trial whatever.

Dr. Robert C. Jamieson, Detroit: I had the opportunity to see most of the patients Dr. Shaffer mentions, in the hospital in Detroit. Most of them were city patients who had been treated with arsenic, in most instances with too much of the drug. The great majority of the patients were received at the hospital with marked dermatitis, with the exception of the two Dr. Shaffer mentioned who had the nine-day type. Shortly after their admission such intense edema developed that intravenous medication was almost impossible. It had been the custom to administer sodium thiosulphate intravenously, with the varying results with which you are all familiar. In a few cases my associates and I tried to administer sodium thiosulphate orally, securing almost as good results as we had been obtaining from the intravenous injections. After using the dextrose medication we were struck by the immediate results and by the marked reduction of the patient's stay in the hospital. That, I think, is very important, particularly in a city hospital where it is extremely necessary to cut down expenses. On account of the difficulty in giving this treatment intravenously, I think that if some other method of administering it can be found a very important step forward will have been made. If the dextrose can be administered orally or rectally, it will add a great deal to the treatment.

As far as thromboses are concerned, they could be obviated if the injections were given very slowly after withdrawal of the blood mixed with the dextrose, much more time being used in the administration of the dose of 20 cc.

I have had much the same experience as Dr. Shaffer in treating private patients, and I think that the method should have a further trial.

Dr. Bedford Shelmire, Dallas, Texas: One should be aware of the severe reactions which may follow the indiscriminate use of sodium thiosulphate, a drug which is itself capable of causing a generalized exfoliative dermatitis.

About two years ago severe dermatitis developed in a patient with scabies within twenty-four hours following the use of a 6 per cent sulphur salve. The application of a 1 per cent sulphur ointment some months later produced a typical dermatitis on the sites of contact. After an interval of one year the patient was induced to subject herself to the intravenous injection of 50 mg. of sodium thiosulphate (sulphur content, approximately 3 grains [0.19 Gm.]). The purpose of this experiment was to determine whether the intravenous injection of a drug would cause dermatitis in a person whose skin was sensitive to the external application of the same drug. It is a well known fact that persons whose skin is markedly idiosyncratic to ivy can usually ingest the leaves or the extract of this plant with impunity.

Twenty-four hours after the patient was given 50 mg. of sodium thiosulphate intravenously, a marked swelling of the face and extremities occurred, and there appeared a generalized papular rash. This rapidly became confluent. Within ten days the cutaneous picture was that of a generalized exfoliative dermatitis,

clinically indistinguishable from that produced by arsenic. Complete healing required approximately ten weeks. Therefore sodium thiosulphate is capable of producing a generalized exfoliative dermatitis in a patient sensitive to sulphur.

Dr. Sigmund Pollitzer, New York: I have not seen a case of arsphenamine dermatitis in my practice in the course of fifteen or sixteen years. I do not continue the use of arsphenamine over a period of six or eight weeks, as is commonly done. I give a full dose on each of three successive days, followed by a course of treatment with preparations of the heavy metals, and if necessary, I give another three-day course of arsphenamine later. I know that many are afraid to use this method, but I wish they were not. There is no disturbance following three or even four doses on successive days.

Dr. Loren W. Shaffer, Detroit: I appreciate the suggestion of Dr. Dennie regarding transfusions. I prefer to leave the question of sodium thiosulphate to further investigation. My own feeling is that it has little value after four or five days. Dr. Jamieson's suggestion regarding the oral administration of dextrose is discussed in the paper. I do not think it necessary to take the precaution of withdrawing blood into the syringe in giving dextrose. I feel that if the injection is given very slowly there should be no difficulty, provided the needle gets into the vein.

As to the question of new cases, I think it is the experience everywhere that if one recognizes the early manifestations of dermatitis and stops treatment at once, true dermatitis exfoliativa can be prevented. In city hospitals, to which the patients come from many sources, and among the patients of doctors who do not recognize or heed the early signs of danger cases still occur in fair numbers and require treatment.

ETIOLOGY OF GRANULOMA ANNULARE

WITH SPECIAL REFERENCE TO THE TUBERCULOUS THEORY

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The clinical and histologic features of granuloma annulare are well defined and leave little for discussion. On the other hand, its cause has been a subject for active discussion for many years. The center of the argument has revolved around the moot question of its tuberculous origin, which was first raised by Brocq and Little in the early years of the present century. Today, opinions about the rôle of tuberculosis in granuloma annulare differ widely. Perhaps the trend toward a belief in the tuberculous origin of the disease has become definite in recent years, but there are still many who regard the question as fairly open.

This article is an attempt to marshal all pertinent evidence on the subject and to present it as succinctly as possible. Opinions have been given less heed than clinical and laboratory investigations. The fact that nowhere in American literature on dermatology has an attempt been made to present and analyze the literature on the etiology of granuloma annulare seems to make the present endeavor worth while. Eight cases of the disease form the basis of this report.

REPORT OF CASES

CASE 1.—L. G., a girl, aged 7 years, was first seen on Feb. 13, 1928. Her mother stated that the eruption was first noticed in June, 1927. At that time three small nodules had been observed on the right buttock. These had gradually enlarged and in the course of three or four months had developed into annular lesions. The enlargement appeared to be progressive and about equal in all of them. The child had not complained of itching or other subjective sensations, and as she was in apparently good health a physician was not consulted.

Both parents were living and well, and there was no history of tuberculosis in the family. The patient was an only child. Her only known contact with tuberculosis was about a year before the lesions appeared, when she had a playmate who had contracted pulmonary tuberculosis. The patient had had measles and varicella during her third and fourth years and occasional attacks of sore throat.

She was referred to a pediatrician for study. Examination revealed a height-weight ratio showing 10 per cent undernourishment. There was no lymphadenopathy. Examination of the head showed only chronically inflamed and moderately hypertrophic tonsils and adenoids. The heart was normal. Except for a spastic

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colon, which was palpable throughout its length, the abdomen gave no evidence of abnormalities. The lungs were found to be normal, on both physical examination and roentgenographic study. A blood count showed 80 per cent hemoglobin, 4,080,000 red cells and 8,800 leukocytes. A differential white cell count showed 47 per cent polymorphonuclears, 51 per cent small mononuclears, 1 per cent large mononuclears and 1 per cent eosinophils. Urinalysis showed nothing abnormal. The blood gave a four plus positive reaction to the Wassermann test. An intracutaneous tuberculin test (0.00025 human and bovine old tuberculin) gave negative results on twenty-four and forty-eight hour readings, and there was no general or focal reaction.

Examination of the skin showed three lesions on the right buttock and one on the left buttock, another on the web between the second and third fingers of the right hand and one near the umbilicus. These lesions were typical of the disease, being annular, with a firm, raised outer rim enclosing a practically normal inner zone. The largest lesions were on the buttocks, the smallest, on the hand. The latter had escaped the notice of the mother.

The patient was treated with roentgen rays, a diet high in vitamins, cod liver oil and neoarsphenamine. Within two months all the lesions disappeared, and the Wassermann reaction gave negative results. However, in two weeks the efflorescences recurred at their former sites. During April, 1928, two lesions appeared on the right leg and one on the left. Biopsy was performed on one of the lesions on the right leg after it had been present for about four weeks and had assumed the characteristic annular appearance. During July and August, 1928, bismarsen was substituted for neoarsphenamine and mercury. By the end of the latter month the cutaneous manifestations had disappeared, but they reappeared at irregular intervals until March, 1929, when the patient left my observation. Antisyphilitic medication had been continued until that time. Several Wassermann reactions were negative up to the time of her disappearance. Except for the roentgen ray treatment, which had been given during the original attack and the first recurrence, the disease was not treated. In view of the fact that antisyphilitic treatment was given with difficulty to the rather rebellious child, I refrained from using painful local measures, such as carbon dioxide snow, for the much less important skin disease. In December, 1931, the mother reported that there had been no evidence of granuloma annulare for at least two years.

Microscopic study of the removed specimen revealed the characteristic necrotic focus surrounded by a zone of infiltrating cells. Examination of many sections stained by the Ziehl-Neelsen method showed no acid-fast organisms.

Case 2.—R. S., a girl, aged 10 years, was first seen on June 6, 1929. She was unusually healthy and robust in appearance. About a year previously her mother had noticed a small papule over the external malleolus of the right ankle. This had gradually enlarged and had become annular. Several months after the appearance of the first lesion, a second had appeared in close proximity and had followed the same course. Neither had occasioned any subjective symptoms.

The family history was entirely negative for tuberculosis, and the patient, so far as was known, had never come in contact with any one with that disease. She had had pertussis during her second year, varicella during her sixth and measles during her eighth. When she was 6 years old her tonsils and adenoids had been removed. At the time of the onset of the skin disease her general health and functions were normal, and they had continued so.

The eruption consisted of two roughly circular, closely adjacent lesions on the external surface of the right ankle. The larger lesion was 6 cm. in diameter; the

smaller was not quite half that size. Except for size, they were similar, exhibiting a firm, cordlike, moderately raised periphery enclosing skin which was normal except for a bluish-brown tint. Under diascopic pressure the peripheral wall blanched and the central area paled to a faint brown. Sensation in the affected areas was normal.

A general physical examination made by a pediatrician showed a well developed, muscular, active child. No visceral abnormalities were noted. Roentgenograms of the chest revealed no signs of tuberculosis. A blood count and urinalysis were normal, and the Wassermann reaction was negative. Intradermal tests with old tuberculin in dilutions of from 1 : 1,000,000 to 1 : 100 gave negative results.

Biopsy of a section from the periphery of a lesion showed a normal epidermis and upper cutis. From just above the level of the sweat glands and extending almost to the subcutaneous fat there was a large number of infiltrating cells arranged in clumps or strands between the collagenous bundles. These cells were chiefly epithelioid, with a small number of lymphocytes. One small area of the section showed incomplete and indefinite necrosis and was surrounded by a few fibroblasts and epithelioid cells. The histologic picture was not typical of granuloma annulare; neither was it suggestive of other granulomas that might come under consideration. In view of the fact that several other cases of granuloma annulare without central necrosis have been recorded (by Dubreuilh, Adamson, Pellier and others) and that Arndt[1] did not consider central necrosis very important, it seems permissible to enroll this case with those already mentioned as clinically typical and histologically atypical.

Case 3.—M. H., a girl, aged 14 years, was referred on April 11, 1931, by Dr. W. F. Hasskarl of Brenham, Texas, because of a single lesion situated just below the right sternoclavicular articulation. It had been present for three months and had occasioned no subjective symptoms. When first seen, it was annular, according to the mother. Iodine and other remedial agents had been applied, and under this treatment it had almost completely disappeared. However, it had begun to develop about a month before the patient consulted me, but in place of being rounded it had assumed a semicircular contour.

There was nothing in the patient's recent medical history to account for its appearance; as a matter of fact, she had been in unusually good health during the previous year.

There was but one instance of tuberculosis in the family: A maternal aunt had pulmonary tuberculosis; but the patient had never been in contact with her.

The patient was high-strung and slender; she had no disorders except the skin disease. She had had pertussis at 3 years of age and rubella at 11. She had not yet menstruated. General physical examination revealed no abnormalities, except a suspicious chronic tonsillitis. Her height was 5 feet, 1½ inches and her weight was 107 pounds. Special attention was given to her chest. Except for an increased whispered pectoriloquy, nothing abnormal was noted. Stereoroentgenograms of the lungs showed a moderate chronic passive congestion but no evidence of tuberculosis. An intracutaneous tuberculin (1 : 1,000) test gave negative results. A blood count and urinalysis showed nothing significant, and the Wassermann test gave negative results.

The lesion was located just below the right sternoclavicular articulation. It was semicircular, with the convexity downward, and consisted of a firm, cordlike,

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1. Arndt, G., quoted by Brun, A.: Ein Beitrag zur Kenntnis des Granuloma annulare (Radcliffe Crocker), Arch. f. Dermat. u. Syph. **135**:117, 1921.

slightly raised rim outlining a moderately reddened field of otherwise normal skin. The hyperemic area faded imperceptibly into the unaffected surrounding area. The raised border, which was also moderately red, became wax-white under diascopic pressure.

No biopsy was permitted. The lesion had almost completely disappeared under therapy with filtered roentgen rays when the patient was last seen, on May 28.

CASE 4.—T. H., aged 2½ years, the son of a physician, was first seen on Sept. 13, 1928, because of an eruption on both legs, which had been present for three or four weeks. There were several small papular and annular skin-colored lesions which were firm to the touch; the annular ones presented a cordlike periphery. A diagnosis of probable granuloma annulare was made. The patient was not seen again until February, 1929, when he presented a new lesion on the back of the left hand and several new ones on each leg. The original efflorescences were still present but were larger, the nodular ones having become annular.

In the interval since the first visit he had been seen by several dermatologists in New Orleans, who had made a diagnosis of leprosy but had been unable to substantiate it by laboratory examination. In fact, the clinical pathologist to whom he had been sent, Dr. Foster Johns, told me that he was certain from a study of the case that the condition was not leprosy. The patient was also examined by several dermatologists in Houston, who agreed with my diagnosis of granuloma annulare. The lesions have never exhibited anesthesia. The patient has had practically no treatment (two treaments of 1 unit each of roentgen rays and a small amount of solution of potassium arsenite), and the eruption has at times disappeared for some months and then recurred. The individual lesions have always followed the same course and have exhibited the same characteristics, being small skin-colored papules gradually enlarging into ring-shaped lesions. At the height of development they average 3 cm. in diameter. They remain for months.

A complete physical examination and laboratory studies revealed no evidence of tuberculosis. There is no tuberculosis in the family. The results of a tuberculin test (old tuberculin administered intradermally in a dilution of 1:1,000) on April 15, 1931, were negative. A roentgenogram of the chest, taken on Sept. 18, 1928, showed no changes suggestive of tuberculosis. A second roentgenogram was taken in February, 1930. The findings were normal, except for a small calcified gland in the right hilus, which had apparently not been present at the time of the first examination.

An early lesion was removed, and a few sections were stained with hematoxylin-eosin and many with Ziehl-Neelsen's stain. The latter revealed no acid-fast bacilli. The epidermis was normal. Beginning in the upper third of the cutis and extending to the subcutaneous fat, there was a pronounced cellular infiltration, which was arranged in foci or in strands. The coil glands and ducts were surrounded by the infiltration, but otherwise appeared normal. The character of the infiltration varied; in some foci epithelioid cells were present almost exclusively; in others, lymphocytes predominated, while in some areas the two types were intermingled in fairly equal numbers. In some areas the infiltrating cells were separated by intercellular edema. The collagenous structure was disrupted in places, but there was no evidence of a necrotic zone. The histologic picture lacked the characteristic features of granuloma annulare. Nevertheless, I included the case in this report as one of granuloma annulare because no other diagnosis is acceptable and because it probably represents an example of granuloma annulare without necrosis.

CASE 5.—B. L., a boy, aged 11 years, was seen in April, 1928, because of an annular lesion directly over the left patella and about the size of that bone. It had appeared after a bruise about two years previously and had gradually enlarged. When it was first examined, the border was cordlike, unbroken and practically circular and enclosed a slightly brownish, shagreen center showing some branny scaling which may have resulted from local applications. There were no subjective symptoms. Clinically, the lesion was characteristic of granuloma annulare.

The family history revealed that a maternal aunt had tuberculosis of the eye. The patient had never had any evidence of tuberculosis. He was well developed, active and apparently in excellent health.

He was examined by a pediatrician, who reported normal physical findings. Nothing suggestive of tuberculosis was noted. Routine laboratory examinations showed no abnormalities. Intradermal tuberculin tests with both human and bovine strains gave negative results. A stereoroentgenogram of the chest showed nothing abnormal.

Biopsy was not permitted.

CASE 6.—J. B., a girl, aged 14 years, was seen on Sept. 29, 1930, because of an eruption of about one year's duration. On the dorsum of the right foot there was a single annular lesion about 6 cm. in diameter, with a raised, firm, moderately reddened cordlike border enclosing an objectively normal central zone. On the dorsum of the left foot were three smaller lesions showing similar features. The lesions had begun as papules; they had gradually and progressively increased in size but had produced no subjective symptoms. The onset and course of the disease had been unattended by any systemic illness or symptoms.

The family history was free from tuberculosis. The patient had had pneumonia when she was 2 years old and had had her tonsils removed when she was 11. She had never been intimately exposed to tuberculosis. She appeared to be a healthy, normally developed child.

She was referred to an internist for a thorough examination with special reference to tuberculosis. A complete physical examination, the usual laboratory procedures and a roentgenogram of the chest revealed nothing abnormal. An intradermal tuberculin test (old tuberculin in a dilution of 1:1,000) gave frankly positive results; in dilutions of from 1:10,000 to 1:1,000,000 there was no reaction. No biopsy was performed. The disease disappeared after several exposures to filtered roentgen rays. It recurred several months later and again responded to this treatment.

CASE 7.—M. B., a man, aged 55, was seen on Feb. 4, 1929, because of a typical annular lesion on the dorsum of each hand. These had been present for about one year.

His family history was negative for tuberculosis, and he had never had prolonged contact with a sufferer from that disease. When he was 26 years old his health had become "run down"; tuberculosis was suspected at the time but was never proved. He had never had a serious illness, but had suffered for many years from migraine.

Physical examination by an internist revealed a well nourished man in good condition. Nothing abnormal was noted on examination of the heart, lungs and abdominal viscera. There was low grade chronic prostatitis. Roentgenograms of the paranasal sinuses gave normal findings, while a roentgenogram of the chest showed thickening of the bronchi and several old calcified hilar lymph glands.

The Wassermann reaction was negative. Urinalysis and a blood count gave normal findings. Intradermal tuberculin tests (old tuberculin in dilutions of from

1 : 1,000 to 1 : 100,000) gave frankly positive reactions. There was no focal reaction and no apparent systemic reaction. The temperature was not taken.

After receiving 2½ units of unfiltered roentgen rays, without an appreciable effect on the lesions, the patient disappeared and was not seen again until December, 1931. The original lesions were still present and had enlarged considerably, and three new lesions had appeared. All presented the characteristic firm, elevated, cordlike border surrounding a slightly brownish central zone. The most recent lesion, which was approximately of six months' duration, was excised; half was inoculated into guinea-pigs, and the remainder was stained with hematoxylin and eosin (a few sections) and with Ziehl-Neelsen's stain. The guinea-pigs were killed two months after inoculation and showed no evidence of tuberculosis.

Histologic study revealed the characteristic architecture of granuloma annulare. In the sections stained with Ziehl-Neelsen's stain no acid-fast organisms were found.

Case 8.—Mrs. L. S., aged 37, was first seen on Aug. 29, 1927, because of a single lesion situated just below the left elbow. This had been present for six months; it had begun as a firm papule the size of a pea and had gradually enlarged and changed to a half circle. It had occasioned no subjective sensations.

The patient's family history was negative for tuberculosis. She had been married for fifteen years and had two healthy children. She had never been seriously ill. The lesion had not been associated with any change in health or functions. There were no disorders referable to the internal organs.

The lesion was a semicircular, wax-colored, moderately raised, firm band about ½ inch (1.27 cm.) from tip to tip. It was freely movable with the skin and was composed of small, indistinctly outlined papules. The patient was told that the probable diagnosis was granuloma annulare, but she refused treatment.

She returned about a year later. In the meantime, radium had been applied by another physician. The original lesion had vanished, but four new ones had appeared on the extensor surfaces of the forearm. They were firm, dome-shaped, wax-colored papules about 4 mm. in diameter. None showed any evidence of a tendency toward annular configuration.

She was referred to her physician, Dr. M. L. Graves, an internist, for a thorough medical survey. He reported negative results, except for healed apical tuberculosis in the left lung and slight pelvic tenderness, which he did not regard as important.

The patient then disappeared for about seven months. On her return she presented several new lesions, all small papules, situated on the neck, scapulae, the dorsum of the right hand and the left wrist. One of the papules was removed for microscopic study. It revealed the typical structure of granuloma annulare: a central necrotic zone in the midcutis surrounded by a zone of epithelioid cells and lymphocytes.

The subsequent course of the disease, to the time of writing, was briefly, as follows: The patient received roentgen ray treatment and neoarsphenamine conjointly. Although the lesions which were treated by irradiation disappeared, new ones developed.

In January, 1930, another search for active tuberculosis and a focus of infection revealed neither. At this time a Mantoux tuberculin test (human strain) gave strongly positive reactions in dilutions up to 1 : 100,000. There was a slight general reaction consisting of malaise and elevation of temperature as high as 99.8 F., but no focal reaction.

A small lesion of three months' duration was removed; half of it was prepared with the Ziehl-Neelsen stain, and the other half was inoculated into guinea-pigs. Both procedures resulted negatively.

In the fall of 1930 the patient went to the Mayo Clinic, where the diagnosis of granuloma annulare was confirmed. A microscopic study made there again showed the characteristic architecture of that disease. Thorough examination revealed no evidence of active tuberculosis. The tonsils were considered infected, and their removal was urged, but the patient refused her consent.

At Dr. W. H. Goeckerman's suggestion, she was given injections of gold and sodium thiosulphate intravenously. She received twelve injections (a total dose of 280 mg.), without result. During this treatment, the typical annular configuration developed in a lesion on the neck, and the patient was treated by the injection of a 1 per cent solution of gold and sodium thiosulphate given intramurally. This resulted in the disappearance of the lesion. In February, 1931, the Mantoux test was again performed, with the same results as in the previous year.

The patient disappeared until February, 1932. During her absence a few new lesions had appeared. She was given injections of tuberculin, beginning with a dosage of 0.1 cc. of a 1 : 100,000 dilution. The doses were increased rather rapidly. After the seventh injection the lesions began to involute, and after the seventeenth injection (0.15 cc. of a dilution of 1 : 1,000) they disappeared.

In March 18, 1933, she reappeared with a single new lesion of a few weeks' duration. She was given 0.05 cc. of a 1 : 1,000 dilution of old tuberculin subcutaneously. This produced a pronounced local and a mild systemic reaction but no focal effect. The lesion disappeared within two weeks.

Summary of Cases.—All the cases were clinically typical, but there is some question of the diagnosis in cases 2 and 4 because of atypical histologic pictures and in cases 3, 5 and 6 because no tissue was examined. In the three remaining cases the diagnosis is unquestionable.

In none of the patients was there any demonstrable evidence of active visceral tuberculosis. In cases 3 and 6 there was a family history of tuberculosis. In case 7 active tuberculosis was suspected years before the onset of the disease, but this was never proved. In case 8 the patient revealed healed apical tuberculosis.

The inoculation of guinea-pigs gave negative results in two cases. It should be remarked here that the animals were killed two months after inoculation through ignorance that in inoculation of suspected tuberculosis of the skin the animals must be observed for at least six months before reliance can be placed on negative findings (Calmette).

Examination for acid-fast bacilli in sections from lesions in four cases (1, 4, 7 and 8) gave negative results. Tuberculin tests with the Mantoux method gave negative results in five of the children and positive results in one. They revealed a high degree of allergy in the two adults.

The gist of these findings is that active tuberculosis was not present in these patients and that the attempts to demonstrate a relationship of the skin disease to tuberculosis were unsuccessful so far as they went.

REVIEW OF THE LITERATURE

The two absolutely conclusive demonstrations of tuberculous infection in a skin disease are the finding of tubercle bacilli in the lesions and positive results in the inoculation of guinea-pigs. Failing these positive proofs, circumstantial evidence must be invoked. This evidence, in the main, must be the association of visceral tuberculosis with the disease, the simultaneous presence of known tuberculous disease of the skin and granuloma annulare, the reaction of patients with the latter disease to tuberculin (including focal reactions) and the histologic structure of the lesions.

Proceeding on this basis, the first point to be considered is the presence of tubercle bacilli in the lesions of granuloma annulare. Many attempts have been made to demonstrate these organisms in the tissue. Arndt [1] was uniformly unsuccessful and Jacobi [2] in a number of cases. My fruitless search has already been mentioned. Reports of single cases in which search was unsuccessful are fairly numerous and need not be mentioned individually. Dittrich [3] is the only investigator who has recorded the presence of acid-fast organisms morphologically resembling tubercle bacilli in granuloma annulare. He reported positive findings in two cases. The sections were stained by the Ziehl-Neelsen method. Dittrich gave no clinical details of the cases. The patients were adults, and the lesions were of from six months' to two years' duration. The acid-fast organisms were found in the walls of the vessels of the midcutis on a level with the granulomatous foci, in the sound or regenerated cutis and in the necrotic zone. No animal inoculations were carried out, and Dittrich admitted that the lack of such inoculations prevented absolute proof that the organisms were tubercle bacilli. No one has been successful in corroborating this report.

The inoculation of guinea-pigs with material from patients with granuloma annulare has yielded uniformly negative results. According to Jacobi,[2] Volk was unsuccessful in fourteen cases. Negative results were recorded by Ornstein,[4] Nicoletti,[5] Stettler [6] and a number of others. The last author also mentioned the earlier unsuccessful attempts of Arndt.

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2. Jacobi, F., in Jadassohn, J.: Handuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 10, p. 1.

3. Dittrich, O.: Zur Aetiologie des Granuloma annulare, Arch. f. Dermat. u. Syph. **153**:599, 1927.

4. Ornstein, M.: Zur Kenntnis des Granuloma annulare, Arch. f. Dermat. u. Syph. **146**:243, 1924.

5. Nicoletti, V.: Etiopatogenesi del granuloma annulare, Gior. ital. di dermat. e. sif. **71**:1848, 1930; abstr., Zentralbl. f. Haut- u. Geschlechtskr. **36**:800, 1931.

6. Stettler, E. A.: Beitrag zur Kenntnis des Granuloma annulare, Arch. f. Dermat. u. Syph. **132**:314, 1921.

The reaction to tuberculin in granuloma annulare has occasioned some interesting discussion since the conception of positive tuberculin anergy in this disease (along with sarcoid and lupus pernio) by Jadassohn and his school. Jadassohn was struck by the number of negative reactions to tuberculin encountered in patients with sarcoids and lupus pernio, and later observations by investigators of this school led them to include granuloma annulare among the "sarcoid reaction forms" with frequent evidences of positive anergy. The number of cases of granuloma annulare so far studied, however, is admittedly too few to form the basis for definite conclusions. Positive anergy has been so recently discussed by Jadassohn [7] and by Sulzberger and Wise [8] that extended comment on the applicability of this conception to the clarification of the cause of granuloma annulare is unnecessary. It should be said, however, that the theory of positive anergy has not yet been established, though, so far as I am aware, there is no work in dermatology that forcibly speaks against it. American phthisiologists, if one may judge by the recent remarks of Allen K. Krause,[9] seem inclined to be skeptical or, at least, to suspend judgment on this point.

In regard to the reaction of my own patients to tuberculin, the results have already been mentioned. In this small series the results seem to me to be inconclusive and to permit no sound deductions. For example, all but one of the children gave negative Mantoux reactions, though from their ages three or four positive responses were to be expected, while both adults showed pronounced allergy to tuberculin. From certain remarks of Jadassohn, an exquisite sensitivity to tuberculin is to be expected in some cases of granuloma annulare in the early period of the disease, but this highly allergic state is replaced by a negative response (positive anergy) as time goes on. So far, this has not happened in my adult patients, though they have been under observation for several years.

Kissmeyer [10] found negative Pirquet reactions in six patients. Four of his patients were children; two were adults less than 30 years old. He did not believe in the tuberculous origin of the disease and explained the negative reaction to tuberculin by the fact that in Scandinavia about 50 per cent of the population under 30 years of age fails to react to tuberculin.

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7. Jadassohn, J.: Remarks on Tuberculin in Dermatology, Brit. J. Dermat. **41**:451, 1929.

8. Sulzberger, M. B., and Wise, F.: Tuberculin: Newer Dermatological Considerations and Reasons for Its More General Use in Diagnosis, M. Clin. North America **14**:1555 (May) 1931.

9. Krause, A. K.: Personal communication to the author.

10. Kissmeyer, A.: Sur l'étiologie du granulome annulare, Bull. Soc. franç. de dermat. et syph. **38**:64, 1931.

Martenstein and Noll [11] found that of nine patients, four reacted negatively to the Mantoux test, while two gave positive reactions to dilutions of 1 : 1,000 and three gave positive reactions to dilutions of 1 : 5,000, 1 : 50,000 and 1 : 1,000,000 respectively. These investigators, who are members of the Jadassohn school, were the first to group granuloma annulare with the sarcoids and lupus pernio among the "sarcoid reaction forms" of tuberculosis of the skin.

Weber,[12] who apparently doubted the tuberculous origin of the disease, reported three cases in young children who gave negative Mantoux reactions.

In a series of eighty-six cases of granuloma annulare [13] compiled from the literature by me the results of intradermal tuberculin tests were as given in the table. These figures indicate a definitely lower percentage of positive reactions to tuberculin than is found in the population at large. Sulzberger and Wise,[8] for instance, stated that positive

Mantoux Reaction in Cases from the Literature

		Positive	
Age of Patient	Negative	Dilution of 1:1,000	Dilutions of 1:10,000 and Over
1 to 10 years	12	..	..
11 to 20 years	3	3	..
21 to 30 years	4	2	..
Over 30 years	2	3	2
Not given	1	5	..

reactions to tuberculin occur in 10.5 per cent of persons in the first year of life and in 97 per cent by the fourteenth or fifteenth year.

From the clinical point of view, the association of systemic tuberculosis and granuloma annulare is difficult to evaluate from present evidence. In the first place, tuberculous infection may be occult and often undetectable except at autopsy. Again, tuberculous infection is practically ubiquitous. That a certain proportion of patients with granuloma annulare should present clinical manifestations of tuberculosis is to be expected. The significance of this association remains, for the present, conjectural, since the simultaneous occurrence of a widespread disease like tuberculosis and a rare dermatosis like granuloma annulare may be fortuitous. So many cases of granuloma annulare without associated tuberculosis are on record that the significance of the instances in which both disorders are present is impaired.

11. Martenstein, H., and Noll, R.: Statistische Untersuchungen über die Tuberculin Reaktion, Arch. f. Dermat. u. Syph. **158**:409, 1929.

12. Weber, F. P.: A Note on the Suggested Tuberculous Origin of Granuloma Annulare, Brit. J. Dermat. **41**:67, 1929.

13. These cases, which were collected from a complete file of the Zentralblatt für Haut- und Geschlechtskrankheiten, comprise only those in which specific mention of clinical or laboratory evidence of tuberculosis was made.

In all my patients special effort was made to find some evidence of active tuberculosis, with uniformly negative results.

Ornstein [4] reported four cases, in three of which there were no signs of visceral tuberculosis; in the other (an atypical case), a roentgenogram showed some shadows in the hilar gland. Ornstein thought that the negative tuberculin reactions in his two younger patients were especially significant of an absence of tuberculous infection.

This was likewise remarked on by Lemež,[14] the pediatrician, who reported a single case and discussed the relation of the disease to tuberculosis. His patient, a child aged 2½ years, showed no detectable evidence of visceral tuberculosis and gave repeatedly negative reactions to tuberculin. He believed that these findings definitely indicated the absence of tuberculosis.

Brun [15] reported a carefully studied case in which there was no clinical evidence of tuberculosis. He discussed the relationship of granuloma annulare to tuberculosis and apparently found insufficient evidence to convince him of a tuberculous etiology.

Kissmeyer,[10] found no evidence of visceral tuberculosis in ten cases and rejected the theory of the tuberculous origin of the disease as founded on the reasons given by Martenstein and Noll for enrolling it with sarcoid of Boeck, lupus pernio and sarcoid of Darier-Roussy among the tuberculous diseases of the skin, namely, (1) the presence of positive anergy, (2) roentgenographic shadows in the hilus and (3) the presence of anticutins and procutins in the serum of the patients.

Grütz and Horneman [16] reported seven cases, none of which showed any evidence of tuberculosis.

In one of Stettler's [6] three cases, there were suspicious visceral findings.

Of Little's [17] series of forty-nine cases, only one showed pulmonary tuberculosis, and this case was questionable. However, Little advanced the theory of the tuberculous origin of the disease on the basis that the patients were hereditarily tainted with tuberculosis, although they themselves were healthy.

Leschinski [18] had a patient, aged 44, with granuloma annulare and active tuberculous adenitis. Of some significance was the fact that

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14. Lemež, L.: Ueber einen Fall von multiplem Granuloma annulare im Kindesalter, Ztschr. f. Kinderh. **44**:328, 1927.

15. Brun, A: Ein Beitrag zur Kenntnis des Granuloma annulare (Radcliffe Crocker), Arch. f. Dermat. u. Syph. **135**:117, 1921.

16. Grütz, O., and Horneman, E.: Beiträge zur Kenntnis des Granuloma annulare, Arch. f. Dermat. u. Syph. **136**:1, 1921.

17. Little, E. G.: Granuloma Annulare, Brit. J. Dermat. **20**:214, 248, 281 and 317, 1908.

18. Leschinski, A.: Zentralbl. f. Haut- u. Geschlechtskr. **11**:403, 1924.

roentgenotherapy of the lymphoma was followed by disappearance of the cutaneous disease. Pinkus [19] exhibited a patient with granuloma annulare in whom pulmonary tuberculosis was present. He also showed a patient with granuloma annulare and folliclis. He remarked that such cases pointed strongly to the tuberculous origin of the disease.

Burnier and Rejsek [20] recorded a case of the disease in a girl, aged 16, in whom they thought suggestive evidence of tuberculosis was present. They collected eighty-six cases from the literature and found eight in which manifest signs of tuberculosis were present in the patient or his antecedents. No details were given.

Woronoff and Olessoff [21] described a case of granuloma annulare in which there were physical and roentgenographic signs of pulmonary tuberculosis. The patient also had sarcoid and erythema annulare, and the investigators believed that all three cutaneous diseases were based on tuberculosis.

Lortat-Jacob and Legrain [22] recorded a case of granuloma annulare in a patient who had had tuberculous pleurisy and epididymitis about twelve years previously.

Sachs [23] reported a case associated with pulmonary tuberculosis. In this case the lesion had developed at the site of trauma, and the author postulated that tubercle bacillemia was present, with deposition of the organism at the injured point.

Mgebrow [24] mentioned that he had often found glandular and pulmonary tuberculosis in patients with granuloma annulare. He reported a case in which the latter disease was associated with lupus vulgaris and apical tuberculosis.

Lemež [14] collected one hundred and fifty cases of granuloma annulare from the literature, in which the association of this disease with visceral tuberculosis was as follows: in two cases, with scrofulosis; in three, with pulmonary tuberculosis, and in one, with tuberculosis of the hilar glands. The Pirquet test was positive in childhood in sixty-nine of the one hundred and fifty patients. Lemež thought that a strong argument against the tuberculous origin of the disease was the fact

19. Pinkus, F.: Zentralbl. f. Haut- u. Geschlechtskr. **7**:303, 1923.

20. Burnier and Rejsek: Un cas de granulome annulaire, Bull. Soc. franç. de dermat. et syph. **29**:218, 1922.

21. Woronoff, D., and Olessoff, I.: Zur Aetiologie des Granuloma annulare, Acta dermat.-venereol. **7**:164, 1926.

22. Lortat-Jacob, L., and Legrain, P.: Un cas de granulome annulaire, Bull. Soc. franç. de dermat. et syph. **34**:438, 1927.

23. Sachs, S.: Zur Frage des Granuloma annulare, Zentralbl. f. Haut- u. Geschlechtskr. **32**:243, 1930.

24. Mgebrow, M. G.: Granuloma annulare neben Lupus vulgaris, Dermat. Wchnschr. **88**:545, 1929.

that it is more frequent in childhood than in adult life though the reverse is true of tuberculous infection.

I was able to collect fifty-three cases from the more recent literature in which mention was made of examination for systemic tuberculosis. Of these patients, thirty-five were free from tuberculosis, while there were eight patients with active pulmonary tuberculosis, five with questionable cases and two with evidence of healed tuberculosis of the lungs. There was one patient with tuberculosis of the bones, one with a questionable case of this type and one with tuberculous adenitis.

The simultaneous presence of known tuberculosis of the skin and granuloma annulare has been recorded in a small number of cases. These cases, of course, possess considerable significance, though this is somewhat vitiated by the reports of the concomitance of granuloma annulare and dermatoses which are considered definitely nontuberculous, for instance, lichen planus. The simultaneous presence of a skin disease of known etiology and one the cause of which is controversial points with some reason to the existence of the same causative agent, provided the clinical and histologic characteristics do not definitely exclude a common etiology.

Horowitz [25] had a patient with granuloma annulare associated with tuberculids and tuberculous coxitis.

Pick [26] recorded an instance of the simultaneous presence of a papulonecrotic tuberculid and granuloma annulare. The case of Mendes da Costa [27] and of Carol, in which granuloma annulare developed in a scar of healed lupus vulgaris, are suggestive. Likewise, the case presented by Goldschlag,[28] in which papulonecrotic tuberculids, erythema induratum-like lesions and granuloma annulare were simultaneously present, seems significant. Martenstein's [29] case of sarcoid (Boeck) associated with granuloma annulare also points to a common etiologic factor. The case of Woronoff and Olessoff [21] has already been mentioned, as has that of Mgebrow.[24]

The interesting report of Grütz [30] of a patient with granuloma annulare, folliclis and transitional lesions between the two deserves some space. The patient, a boy aged 2½ years, was apparently free from tuberculosis so far as clinical examinations went, and gave a weak positive reaction to both human and bovine tuberculin. However, he had a

25. Horowitz: Zentralbl. f. Haut- u. Geschlechtskr. **17**:271, 1925.

26. Pick, E.: Zur Aetiologie des Granuloma annulare, Dermat. Wchnschr. **79**: 1603, 1924.

27. Mendes da Costa, S.: Nederl. tijdschr. v. geneesk. **69**:981, 1925; abstr., Zentralbl. f. Haut- u. Geschlechtskr. **18**:685, 1926.

28. Goldschlag: Zentralbl. f. Haut- u. Geschlechtskr. **19**:609, 1926.

29. Martenstein, H.: Zentralbl. f. Haut- u. Geschlechtskr. **22**:608, 1927.

30. Grütz, O.: Arch. f. Dermat. u. Syph. **147**:590, 1924.

definite focal reaction, and on the basis of this he was given tuberculin therapy. This was followed by the disappearance of all cutaneous manifestations. Histologically, the lesions of granuloma annulare extended into the subcutis, which was unusual for granuloma annulare but had been previously recorded by Ornstein, who had collected three similar cases. Grütz' study of his case led him to the conclusion that granuloma annulare and the tuberculids are only different steps in the same fundamental process and that there is a pronounced pathologic affinity between granuloma annulare and the tuberculid group.

Gans,[31] who stated that recent knowledge about granuloma annulare made its relationship to tuberculosis more probable, also believed that if the tuberculous etiology could be proved, granuloma annulare stands close to the papulonecrotic tuberculids. Kyrle [32] was entirely noncommittal about the significance of the histologic architecture. He regarded the disease as a granuloma occasionally showing tuberculoid structure but not of sarcoid type. Stettler [6] stated that the presence of a tuberculoid structure in granuloma annulare removed one of the obstacles to the conception of the disease as a tuberculid.

As a matter of fact, while a large majority of the cases of granuloma annulare show the well known histologic picture of that disease (central necrosis with a zone of demarcation composed of epithelioid cells and lymphocytes), there are on record quite a few cases showing a tuberculoid structure with giant cells. Among the more recently recorded ones may be mentioned the case of Lehner,[33] Milian and Périn [34] and Nicoletti.[5] In Rusch's [35] case the histologic structure was tuberculoid, and there was associated lupus erythematosus. Olah [36] recorded a case in which a tuberculoid structure was present and the patient had visceral tuberculosis. Lortat-Jacob and Legrain [22] found a tuberculoid histologic structure in a patient with a familial and personal history of tuberculosis.

The response of granuloma annulare to tuberculin therapy is, in some instances, striking. This may or may not be significant, since it is well known that tuberculin has an unquestionable nonspecific effect. To prevent constant recurrences, this form of therapy was tried in

31. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, p. 547.

32. Kyrle, J.: Vorlesungen über Histo-Biologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer, 1927, p. 191.

33. Lehner: Zentralbl. f. Haut- u. Geschlechtskr. **38**:36, 1931.

34. Milian, G., and Périn, L.: Granuloma annulaire avec lésions histologiques tuberculoïdes, Bull. Soc. franç. de dermat. et syph. **38**:776, 1931.

35. Rusch: Zentralbl. f. Haut- u. Geschlechtskr. **11**:404, 1924.

36. Olah, D.: Orvosi hetil. **70**:837, 1926; abstr., Zentralbl. f. Haut- u. Geschlechtskr. **21**:737, 1927.

case 8 of my series, with a decidedly beneficial effect. The patient remained free from the disease for a year, after which a new lesion appeared. An injection of tuberculin was then given, which caused a marked local lymphangitic reaction, with moderate systemic symptoms. Though no focal reaction appeared, the lesion melted away within about two weeks.

Monash [37] recently reported two cases of disseminated granuloma annulare in which injections of tuberculin were curative in one case and beneficial in the other.

Sézary and Duruy [38] reported beneficial effects from the tuberculin of Vaudremer. They did not think that such results were definite proof of a tuberculous etiology. Gougerot and Arnaudet [39] obtained a cure by the same means. These investigators were ardent advocates of the tuberculous causation of the disease.

There remain for discussion two other concomitant findings that may have some bearing on the present topic. These are a family history of tuberculosis in granuloma annulare and the finding of tubercle bacilli in the blood on culture by the Löwenstein method. The former will be dismissed summarily with the statement that family histories of tuberculosis in granuloma annulare appear to have no definite significance, since they parallel the finding in the population at large. As to the second point of evidence, it is to be mentioned that Kren and Löwenstein [40] found tubercle bacillemia in two of three cases, but Kissmeyer [10] recorded negative findings in five cases, though the blood was sent to Löwenstein. However, the method of Löwenstein has not yet been established, for that reason no sound deduction can be based on the results obtained with it.

COMMENT

Any one who reviews the evidence for and against the tuberculous origin of granuloma annulare will finish with a feeling of uncertainty.

There are many more cases on record in which there was no evidence of coexistent tuberculosis than the reverse. But negative evidence in regard to the presence of active tuberculosis is not especially strong evidence. The reason for this is that tuberculous infection may be present in an active form below the threshold of detectability. Mesen-

37. Monash, S.: Granuloma Annulare Disseminatum: Report of Two Cases, Arch. Dermat. & Syph. **25**:122 (Jan.) 1932.

38. Sézary, A., and Duruy, A.: Sur le traitement du granulome annulaire par le vaccin de Vaudremer, Bull. Soc. franç. de dermat. et syph. **36**:270, 1929.

39. Gougerot, H., and Arnaudet: Granuloma annulaire ou mieux tuberculose annulaire guéri par la tuberculine, Arch. dermato-syph. hôp. St. Louis **2**:307, 1930.

40. Kren, O., and Löwenstein, E.: Wien. klin. Wchnschr. **44**:405 (March 27) 1931; abstr., Ann. de dermat. et syph. **2**:903, 1931.

teric or tracheobronchial glandular tuberculosis may be beyond demonstration. For this reason it is difficult to exclude tuberculous infection, as contrasted with gross, even though incipient, tuberculous disease. This is especially true of adults, because their reaction to tuberculin has little significance.

On the other hand, negative tuberculin tests are of decided value in excluding tuberculous infection in early childhood. This point is of importance in an analysis of the present question. The fact that there are many cases of granuloma annulare on record in early childhood in which no evidence of tuberculosis (including negative tuberculin reactions) was found is strong testimony that in these cases the cause of granuloma annulare was not tuberculosis. In my opinion, the only answer that can be given to such evidence by the proponents of the tuberculosis origin of the disease is to invoke the theory of specific anergy. This is a weak argument, because the whole conception of specific anergy is still on an insecure basis. The fact is that in the light of the present state of knowledge of tuberculosis one must admit that a child who presents no clinical evidence of tuberculous infection and who gives a negative reaction to tuberculin is free from tuberculosis. If this is granted, then one must conclude that granuloma annulare in such a patient is not due to tuberculosis.

It cannot be so definitely concluded that the same admission must be made for adults who have granuloma annulare and completely negative evidence of tuberculosis. Here, perhaps, the hypothesis of specific anergy may be more forcefully invoked.

On the other hand, the instances in which granuloma annulare and active visceral tuberculosis are present offer a difficult problem in interpretation. In comparison with the total number of cases of granuloma annulare on record, these cases are not especially numerous. My feeling about this group of cases is that no sound deductions can be reached in regard to them. Much more impressive are the instances in which a dermatosis of recognized tuberculous origin and granuloma annulare were simultaneously present. These cases are uncommon, but they appear to be increasing in number, probably because their value as evidence is more and more appreciated and justifies their report. Such cases seem to me to be highly significant, and they appear to indicate strongly that the common causative agent of both dermatoses is tuberculosis. This conclusion is obviously strengthened by the fact that the reaction in both cutaneous disorders following the therapeutic use of tuberculin was found to be the same in Grütz' case. It would seem plausible to conclude that there is a group of cases of granuloma annulare in which the evidence for the tuberculous origin is almost conclusive.

In addition to the clinical evidence, there is on record a considerable amount of laboratory research on the relationship of granuloma annulare to tuberculosis. The results have been almost entirely negative. The findings of Dittrich would have been conclusive on the affirmative side had they been supported by positive results of the inoculation of guinea-pigs. They are inconclusive because they remain uncorroborated and because the acid-fast organisms found by Dittrich were not indisputably proved to be tubercle bacilli.

So far as the histologic picture of granuloma annulare is concerned, no sound deductions regarding a tuberculous origin can be formulated. In recent years a tuberculoid histologic picture has been accepted as consonant with a clinical diagnosis of granuloma annulare. But it is now well recognized that a tuberculoid pathologic structure is found in other conditions than tuberculosis.

The course of pathologic events in the disease are endovasculitis and perivasculitis leading to complete obliteration of the affected vessels. This is followed by necrosis of the surrounding tissue. The cellular zone may be looked on as partly a demarcation and partly a regenerative process (Jacobi). The same sequence occurs in the tuberculids and in erythema induratum, and some investigators look on the three diseases as essentially similar processes, the difference in the position of the affected vessels in the cutis being the only distinguishing feature. However, it is not settled that tuberculosis alone is capable of producing such a series of pathologic events, and therefore, as has already been mentioned, the significance of the disease is still under question.

Of some value as evidence in respect to the tuberculous origin of granuloma annulare is its reaction to tuberculin treatment. The response in case 8 of my series was impressive. The rather small number of reported cases in which this treatment was employed precludes unqualified deductions, but my opinion is that the response to tuberculin is significant and cannot be passed over with the simple statement that the effect is entirely nonspecific. The influence of tuberculin therapy on granuloma annulare requires further study.

CONCLUSIONS

1. Cases in the series studied by me produced no evidence favoring the tuberculous origin of granuloma annulare.

2. The literature on this question is reviewed. There are a number of reported cases of granuloma annulare in which a tuberculous etiology appears probable. However, cases showing no apparent relation to tuberculosis are in the majority. The present status of the question may be stated as follows: Granuloma annulare is caused by tuberculosis in some cases; in others, an unknown infectious agent appears to be the cause.

PHYTOPHARMACOLOGIC TEST IN DERMATOLOGY

FURTHER STUDIES AND SOME CRITICAL ESTIMATIONS

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After five years' experience with the phytopharmacologic test, we believe that a third communication is in order for the purpose of a summary to date of results in pemphigus, and as a pertinent corollary to add some critical comments.

Moreover, it gives opportune advantage to direct attention to certain other dermatoses which require elucidation. These conditions have come to our attention because apparently phytotoxic readings have been recorded sufficiently often to awaken more interest in dermatologic diagnosis and pathogenesis and perhaps in etiology. This is something of a compromise with our former communications, and is the result of a more comprehensive study. It will therefore be our purpose to discuss these findings in a general way, in order to place some evaluation on the possibilities of the test. In a previous communication we discussed the difficulties, the disadvantages and the pitfalls [1] of the technic, but we have also stressed the relative advantage of the method because of the personal equation being restricted to a "one-man" test.

Any endeavor to explain these results is beset with speculation rather than fact, and yet estimation of these findings in the light of clinical diagnosis, of factors in the blood serum affecting the test and of other conditions of so-called toxicity may be of interest. Naturally, criteria of these basic conditions are open to much disagreement. We shall discuss some diseases from these points of view.

These not infrequently positive readings in such a designated group of dermatoses would invite primarily the question of variants in well known clinical types. Brocq's brilliant and attractive "Conception

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Read at the Fifty-Sixth Annual meeting of the American Dermatological Association, Inc., Chicago, June 8, 1933.

From the Department of Dermatology, Johns Hopkins Hospital, and the Pharmacological Research Laboratory, Hynson, Westcott & Dunning, Inc.

1. Pels, I. R., and Macht, D. L.: Phytopharmacology of Pemphigus and Other Dermatoses: Additional Studies, Arch. Dermat. & Syph. **23**:601 (April) 1931.

générale des dermatoses" [2] suggests many illuminating thoughts, and his "faits de passage" might readily be applied here if we could base our study both on morphologic grounds and on the results of phytotoxic studies. Thus the possible transitional phases of bullous erythema multiforme and pemphigus, of dermatitis herpetiformis and pemphigus, of acute disseminated lupus erythematosus with bullae and pemphigus, of the Senear-Usher syndrome and pemphigus, of traumatic bullous dermatoses and pemphigus, of nondescript toxic bullous dermatoses and pemphigus, and the like, open vistas of speculation which are very interesting. The phytotoxic test being apparently occasionally positive in either or both of these coupled conditions certainly tempts one to consider the clinical phases either of transition to pemphigus or at least of a close relationship to pemphigus. Unfortunately, we have as yet no scientific laboratory findings for linking these various dermatoses in a closer relationship. Nor would it be proper to use the phytopharmacologic findings as a basis for a closer relationship except from the standpoint of a relative toxic condition of the blood.

We naturally raise the query whether certain conditions of the blood in dermatoses other than pemphigus exist as recognizable when we obtain low (positive) readings. Aside from the fact that (as will be noted) the toxicity of the blood in these special dermatoses is almost as low as in pemphigus, and aside from the fact that a more circumspect standard of clinical (and laboratory) diagnosis is demanded of us, we are confronted with the problem of a consideration of this toxic factor in the blood of persons with pemphigus and with the other dermatoses.

Thus it brings up the question of what toxicity is, which may be discussed in the narrowed sense of this laboratory procedure. The word toxin, as used in this research, is a strictly scientific term denoting some substance, an organic or inorganic chemical of known or unknown nature, which is present in the blood and has an injurious effect on a living biologic test object. This term, of course, is a relative one. The action of any poison or toxin depends on three factors: the chemical substance itself, the biologic test object and certain external conditions. In our phytopharmacologic studies we have had the good fortune to deal with substances (present in the blood serum) which are not especially harmful for animal protoplasm but are very injurious for living plant protoplasm. By the term toxin, as applied to pemphigus and allied disorders, we therefore mean the presence of (1) certain chemical substances in the blood serum of patients which are (2) injurious to living seedlings under certain conditions, namely, (3) when the seedlings are grown in definite plant physiologic solutions at low temperatures.

2. Brocq, L.: Ann. de dermat. et syph. **8**:65, 1927.

Bearing in mind all the considerations discussed, we may state that even at this early stage the phytopharmacologic studies on diseases of the skin have already led to interesting findings. The phytotoxic test has contributed to a larger knowledge of the etiology of pemphigus.

RESULTS

Approximately 750 additional specimens of blood were studied. The clinical diagnosis was that which was submitted by various colleagues and by ourselves. It may be surmised that some of these diagnoses were open to doubt. For example, many of the specimens were labeled suspected pemphigus, pemphigus to be considered or pemphigus to be ruled out. Certainly a number of dermatoses were classified under the uncer-

*Phytotoxic Index in Pemphigus and Dermatoses of Toxic Origin**

	Number of Specimens	Phytotoxic Index, per Cent
Pemphigus	155	60.9
Previously reported	78	56.7
Total number	233	58.8
Dermatoses of toxic origin with and without bullae	110	61.9
Excluding		
Dermatitis herpetiformis	22	69.5
Senear-Usher syndrome	7	72.4
Senear-Usher syndrome	3	54.3
Total number	10	67.0
Erythema multiforme	21	69.9

* Approximately 750 additional specimens of all kinds were studied.

tain term of erythema multiforme with bullae or erythema multiforme due to drugs. Our greatest problem was to classify specimens with two or more diagnoses and others in which pemphigus was not considered. We placed them in the large group of dermatoses of toxic origin, with or without bullae. A certain amount of rechecking of readings on repeated specimens, follow-up readings and the clinical progress (recovery or death) has permitted a somewhat more accurate but incomplete allocation of such dermatoses.

When readings were very toxic (e. g., 50 per cent) and when the addition of chemicals was suspected, the results were discarded. We repeatedly noted specimens of blood that were apparently free from chemicals but were laked, dark, decomposed and otherwise changed, even when other specimens taken at the same time from the same patient were unaltered. We cannot as yet offer satisfactory reasons for such changes.

The variability of the phytotoxic index in the same patient, when available, has occasionally complicated the final verdict in diagnosis.

However, we have been enabled to confirm a diagnosis of pemphigus by repeated tests and by the report of a fatal outcome. Contrariwise, an initial normal reading in certain bullous dermatoses became toxic in tests in which the diagnosis of pemphigus eventually could be confirmed. Such specimens were originally labeled either dermatitis herpetiformis or suspected pemphigus. Two patients with suggestive pemphigus (and other diagnoses) had repeated toxic indexes, and remained well; other patients, to our knowledge, recovered. Such findings raise the question of the existence of a benign pemphigus as well as of the possibility of recovery in pemphigus. It is a puzzling problem.

The occasional variability of the phytotoxic index in any one disease has not been in direct ratio to the intensity of cutaneous change, and we are at a loss to explain it.

PEMPHIGUS

Naturally, our most interesting findings are still concerned with pemphigus. The only reference abroad to this work has been made by two Italian observers. Their results did not confirm ours.

Bertaccini,[3] who considered the test of little practical worth, according to his experience, apparently did not follow accurately the necessary technic, nor did he study a sufficient number of cases.

Ambrogio,[4] however, found an inhibition of plant growth in pemphigus, but, in addition, his experiments exhibited the same inhibition in other dermatoses. A critical study of his communication revealed that he followed the prescribed method of testing, but instead of growing the seedlings in plant physiologic solution containing the blood serum, he raised Lupinus albus in earth on which he poured the specimen of blood to be examined. The worthlessness of such a technic is quite evident to any one familiar with the experimental methods of plant physiology.

We have made repeated experiments to discover the effect of the addition of very toxic blood serums, such as those in pernicious anemia, leprosy or pemphigus, to sand and soil in jars in which seedings of Lupinus albus were grown, and practically no inhibition in the growth of the plants was noted in any of these cases. The same was found to be true even in case of certain complex organic mercurial compounds and other chemicals, solutions of which were likewise poured over seedlings grown in soil. The explanation is not far to seek; colloidal solutions such as blood are readily adsorbed by the humus and sand and very little of the poison or toxin is absorbed by the roots of the seedlings. In performing the phytopharmacologic test, great care must be exercised in preparing accurately a definite plant physiologic solution containing absolute quantities of the various salts to be used. Even the test tubes in which the seedlings are suspended in solution must be made of hard glass in order to avoid the effect of alkalis which might otherwise be dissolved from the glass.

3. Bertaccini, G.: Boll. d. Soc. ital. di biol. sper. **6**:384, 1931.
4. Ambrogio, A.: Riun. Soc. ital. dermat., Genoa, October, 1931.

For successful performance of phytopharmacologic work, the investigator must be trained not only in the methods of pharmacology but also in those of plant physiology; and in order to eliminate the personal equation and obtain consistent readings, he must have had a great deal of practice. Furthermore, great care must be used in selecting fresh seeds of Lupinus albus. These seeds must be soaked properly and germinated in a suitable medium with only a certain amount of moisture and special conditions of light and temperature. The plant physiologic solution must be prepared accurately from chemically pure salts. In selecting the seedlings for the test, it is well to "match" them as closely as possible and to use a large number to obtain an average reading. The seedlings must be incubated at low, constant temperature and in the dark. Other details regarding technic cannot be given here.[5] Undoubtedly the failure of those who have attempted to perform this test was due to lack of training and acquaintance with the fundamental sciences which underlie the study of phytopharmacology.

Blood from patients with pemphigus received for phytopharmacologic study has been found by us to exhibit a number of characteristics differentiating it from blood specimens obtained from patients suffering from other diseases. Thus, for instance, we have found that when whole blood is sent for examination for pemphigus, the red corpuscles have a tendency to disintegrate so that the blood becomes hemolyzed more quickly than it does in case of pernicious anemia; often decomposition goes further and the blood specimen turns a deep purple. Such samples are unfit for the phytopharmacologic test. We have also found that blood serums from persons with pemphigus are much more readily affected by heat than the serums obtained during menstruation and from persons with pernicious anemia and leprosy. Even on standing at room temperature from twenty-four to forty-eight hours, the blood serum from persons with pemphigus becomes markedly detoxified. The effect of light on this serum is not as marked as it is in the case of serum in pernicious anemia; nevertheless, we take the precaution of keeping all specimens sent for examination in the dark in the ice chest.

In our laboratory, each sample of blood is tested on ten individual seedlings, and an average reading of all is obtained. The same sample of blood is tested over again the following day on ten other seedlings, and, if necessary, the test is repeated until the mean readings obtained on successive days vary no more than 5 per cent. To perform such a large number of tests on higher animals, say, cats, rabbits or dogs, is practically prohibitive.

The group of specimens included those from cases with a clinical diagnosis of pemphigus. In some instances, 2 specimens were run separately and occasionally repeat specimens were tested. It was considered that this would give a better average.

One hundred and fifty-five additional specimens gave an average of 60.9 per cent.[6] The total number of tests (233) gave an average of 58.8 per cent. This average approximated closely our previous figure of 56.7 per cent in 78 specimens.

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5. (*a*) Macht, D. L., and Livingston, M. B.: J. Gen. Physiol. **4**:573, 1922. (*b*) Macht, D. L.: J. Pharmacol. & Exper. Therap. **29**:461, 1926. (*c*) Pels and Macht.[1]

6. Some of these included normal readings (about 15 per cent).

We must assume that the clinical diagnoses sent in were correct, but some of these were open to doubt. Unfortunately, on account of no complete follow-up, we cannot comment on the intensity of disease as compared with toxicity of the serum; but, as stated elsewhere, we know from some experience that the relationship is not a direct one.

All types of pemphigus were included, the majority being vulgaris. Normal readings were occasionally obtained in pemphigus foliaceus, and positive readings (the patients recovering) in so-called pemphigus benignus. A fair number of cases of ocular pemphigus with and without lesions elsewhere were included (both with normal and with positive findings).

In reading the literature, especially the discussions over the differential diagnosis of pemphigus, one is impressed by the variation in opinion concerning the clinical evaluation of this disease. It is unfortunate that time must be the judge of correctness in diagnosis, and it is regrettable also that the phytotoxic reading cannot function as a sine qua non.

There is some comfort, however, in the thought that certain diagnostic criteria still exist, which, despite toxic readings, will serve to allocate pemphigus and other diseases under discussion. It is hoped, therefore, that with combined critical studies of our readings some help may be given to clinical diagnosis.

DERMATOSES OF TOXIC ORIGIN WITH AND WITHOUT BULLAE

We have arbitrarily chosen the term dermatoses of toxic origin with and without bullae to designate a fairly large group of disorders in which, first, positive readings have not infrequently been obtained; second, the etiology was obscure but suggestive of toxic character, and, third, the resemblance to pemphigus, or symptoms suggestive of it, prompted the reference of blood specimens particularly because of the constant or temporary presence of blebs or of bullae. On account of both positive and normal findings, we placed all such diseases, with a definite or indefinite diagnosis, in this group, and we found in 110 readings an average toxic index of 61.9 per cent, almost the same as that obtained in pemphigus.

Aside from the diagnosis of suspected pemphigus or no submitted diagnosis, other diagnoses were dermatitis herpetiformis, erythema multiforme, disseminated lupus erythematosus, pellagra, leprosy, plumbism, thyrotoxicosis with erythema, suspected drug exanthema, the Senear-Usher syndrome, severe pseudocolloid (with blebs) and maculopapular exanthema.

Unfortunately, we had no satisfactory method of confirming the clinical diagnosis in all cases, such as a complete follow-up, yet repeated specimens in many instances gave fairly consistent results. On account

of the toxic readings in some of these cases, exhibiting blebs and bullae, we might suspect a potential pemphigus, or at least a benign pemphigus, because there were instances of recovery and also a record of no fatal termination (remissions). This aspect of the clinical toxic cases interested us particularly and partly prompted this additional communication.

Therefore, we have learned that, contrary to our first impression, certain dermatoses other than pemphigus, or possibly related to pemphigus, occasionally or consistently present positive phytotoxic readings. The interpretation of these findings naturally opens up the dangerous field of speculation, yet it gives us a foothold to enlarge, if possible, our conception of blood toxicity in at least one specific manner and also to illuminate in a small way our conceptions of the pathogenesis of cutaneous changes.

Without presenting tables, we can state that the variation in the index in certain diseases was striking; that is, both normal and highly toxic figures were found. Fairly consistent toxic figures, however, were found in leprosy [7] and in pellagra, in different stages; in acute lupus erythematosus and plumbism, the figures were both normal and toxic; also in the Senear-Usher disease (usually normal, however). In dermatitis herpetiformis the figures were almost consistently normal. In erythema multiforme, with and without vesiculation, the indexes were both normal and toxic, sometimes depending on the stage of the eruption (e. g., normal on the regression or disappearance of lesions).

Finally, any estimation of the value of positive or toxic readings in those conditions, with the knowledge that normal readings also appear, would naturally raise the question of accuracy, or of confirmation, of the clinical diagnosis. Furthermore, pitfalls in technic and other factors influencing and causing toxicity in the blood stream must be reckoned with, as pointed out elsewhere. Bearing these criteria in mind, we wish to discuss briefly some of these conditions.

Dermatitis Herpetiformis.—In 22 cases with this diagnosis, the average reading was almost normal, 69.5 per cent. This confirms our impression of a normal reading being the rule, but it does not remove the possible clinical relationship to pemphigus, nor would we venture to

7. The serums of persons with leprosy (some of which were obtained in the United States, although the greater number were secured through the courtesy of Professor Chopra, School of Tropical Medicine, Calcutta) were found to produce a marked inhibition of the growth of seedlings, the average phytotoxic index being 47 per cent. The toxic reaction of this blood serum immediately differentiated it from that in two other diseases confused with it, namely, tuberculosis and syphilis. It was found repeatedly that the blood serums in tuberculosis and in syphilis, irrespective of concomitant treatment, produced no toxic reaction; and, indeed, the serums in these two diseases were found to give a higher reading than that obtained with serums from normal human blood specimens (Macht, D. I.: Proc. Soc. Exper. Biol. & Med. **27**:150, 1929)

base any prognostic value on the phytotoxic index in this disease until many more records have been made in order to confirm a normal reading.

The Senear-Usher syndrome has received much interesting comment; in 10 specimens an average of 67 per cent approximately normal was recorded. This included one group of toxic readings (Gilman's case, 54.3 per cent, average [8]). In the controversy [9] over the allocation of this disease, many observers consider the pemphigoid phase as a mere complication or an expression of intensity of reaction on the part of the skin, comparable to lichen planus pemphigoides, pityriasis rosea with blebs, bullous erythema of toxic origin (e. g., drug rashes) and the like. Of course, the number of cases investigated is too small to permit one to draw conclusions. Here again, the variability of the readings, both positive and normal, apparently bears no direct ratio to intensity of cutaneous change.

It may be just as plausible to consider certain types of this syndrome as being pemphigus with complications of lupus erythematosus, seborrheic dermatitis and similar conditions, as to consider them the reverse.

As for disseminated lupus erythematosus, we have tested only a few cases. In 2 almost similar cases, both with toxic readings, small bullae eventually developed in one patient (a woman), who died (autopsy revealing tuberculosis of the suprarenals), while the other patient (a woman) recovered. In a recently observed acute case, the readings were normal, and the patient died within several weeks after the onset of symptoms. It has been our impression that this disease is a toxicosis, usually bacterial, and that this toxicity of the blood may at times give a positive response to the Macht method. Since a toxic reading is not obtained in most infectious diseases, one might speculate on the factors which influence this toxicity when the test reveals its presence. We therefore hope to record the results in a larger number of these types of lupus erythematosus and possibly draw some conclusions.

Erythema Multiforme.—Unfortunately, our findings have varied in that both types of the disease (bullae and herpes iris type) and different stages of evolution were included. Consequently, we have no determining percentage of toxicity of the blood which can be used as representing any particular phase. This difficulty has arisen because we have no standard of clinical diagnosis. Our specimens were labeled erythema multiforme or erythema multiforme with bullae; occasionally, involvement of the mouth (lips, buccal mucosae, etc.) was mentioned; many

8. Gilman, R. L.: The Senear-Usher Syndrome: A Dermatosis Combining the Features of Lupus Erythematosus and Pemphigus, Arch. Dermat. & Syph. **24**:84 (July) 1931.

9. Woodburne, A. R.: Senear-Usher Pemphigus, Arch. Dermat. & Syph. **26**:671 (Oct.) 1932. Taussig, L.: The Senear-Usher Syndrome: A Variety of Lupus Erythematosus, ibid. **27**:498 (March) 1933.

of the cases were of the recurrent type, with remissions, and with a duration of not more than from two to three weeks (which may be taken as the average duration of an acute attack of the herpes iris type). Again, we suspect that numerous instances of erythema of toxic origin, with nondescript macules and probably due to a number of possible agents (bacterial, metabolic, drugs, etc.) were inadvertently placed in this group. Therefore, specimens with a diagnosis of erythema multiforme only were included.

In this connection we refer again to this type of erythema multiforme or of toxic erythema, with and without bullae, as exemplified by F. L., an Italian boy.[1] In 17 tests the average was definitely toxic (63.8 per cent). The disease would reappear as vesicles on the lips, followed by a remission for many weeks. He is still under observation and has been in the hospital for various illnesses, including pulmonary tuberculosis and chronic sinusitis, but has had no recurrence of the eruption. His blood was constantly toxic in the last 7 examinations, with an average of 51.3 per cent. We are at a loss to explain this, except to designate the condition a toxic dermatosis, with remissions. It is not pemphigus, yet such a condition, as all dermatologists know, may be the forerunner of pemphigus.

The average of 21 specimens of erythema multiforme was 69.9 per cent, or practically normal. This confirms our previous readings (22 specimens) of a normal average of 70.5 per cent with the finding that certain specimens occasionally were toxic. In early disease (herpes iris) we have found a positive phytotoxic index which later became entirely normal. This bespeaks a transient toxemia.

Some of these cases with consistent toxic readings have not been completely investigated from the standpoint of organic and functional changes known to produce toxicity of the blood stream, and also of undiscovered factors which might be responsible for the same toxicity.

Thus we may possibly conclude that certain types of erythema multiforme, including the so-called bullous types, bear some relationship to pemphigus, either in pathogenesis or in etiology, or that at some time or other, either at the height of the eruption or after the disappearance of lesions, there is some factor in the blood stream which gives a toxic reading by the phytopharmacologic test.

LABORATORY STUDIES AS APPLIED TO THERAPY

Finally, it has been our constant hope to make some attempts at finding methods of approach to therapy in pemphigus. The phytopharmacologic test lends itself to evaluating various methods in this connection. We therefore wish to make a preliminary and brief statement of some findings

Ludy [10] has claimed that vitamin D is of value in certain diseases of the skin, including pemphigus. In order to discover whether or not this was true in the laboratory, we performed a series of experiments. In the first place, pure ergosterol was dissolved in plant physiologic solution of sodium chloride, and the effect of such a mixture on the growth of lupinus seedlings was determined Other experiments were afterward made on the blood serum of persons with pemphigus. The toxicity of a sample of the serum in physiologic solution of sodium chloride was determined, and then the same specimen was mixed with the ergosterol containing saline solution, and this mixture was also tested for its effect on lupinus seedlings. It was found that traces of pure ergosterol added to a solution of the serum in which lupinus seedlings were grown markedly decreased its toxicity. Still more promising results in regard to detoxification of these serums were obtained in vitro by the use of methylthionine chloride, U. S. P. (methylene blue), in weak concentrations. It was found that even very weak solutions of this dye (1:50,000 to 1:100,000) produced detoxification of these serums when seedlings grown therein were compared with carefully made controls grown in solutions of the dye alone. One of us has described these laboratory findings elsewhere.[11] Whether they will hold good in clinical practice, of course, is purely a matter of conjecture, but, considering the low toxicity of both ergosterol and methylthionine chloride, it is to be hoped that some investigators will cautiously employ small doses of these drugs in treating patients afflicted with pemhigus, a disease for which no rational method of treatment is so far known.

SUMMARY AND CONCLUSIONS

1. Further investigation of toxic dermatoses (some 750 specimens) revealed that the blood serum in various types of pemphigus continued to give a toxic reading by the phytopharmacologic test. The average phytotoxic index was about 60 per cent.

2. It was also found that in a group of dermatoses suggestive of toxic causation and bearing suggestive or striking similarity to pemphigus on account of the presence of blebs or of bullae an average toxic index of 61.9 per cent was also found.

3. The possible relationship of such dermatoses to pemphigus was hinted at, and the transitional stages between these and some clinically well defined diseases also giving toxic indexes were suggested. This refers particularly to certain types of erythema multiforme and other erythematous changes with and without vesiculation.

10. Ludy, J. B., and Devalin, C. M.: Urol. & Cutan. Rev. **36**:817, 1932.

11. Macht, D. I.: Proc. Nat. Acad. Sc., to be published.

4. In dermatitis herpetiformis and the Senear-Usher syndrome, with a restricted number of tests, however, normal averages were obtained.

5. It was again found that there was no direct ratio between toxicity and intensity of disease.

6. Such results naturally suggest an attempt to improve our acumen in clinical diagnosis. Therefore, any proper evaluation of the test in pemphigus must still be based on a conjoined consideration of the clinical symptoms.

7. A recapitulation of the basic principles involved in phytopharmacology, as exemplified by the work of one of us (D. I. M.) in clinical disease, has been given, in order to suggest some working concept for the term toxicity.

8. Finally, studies of blood toxicity have been carried on by one of us (D. I. M.). Results in vitro seemed to indicate that ergosterol has some effect on the toxin of pemphigus. It was also found that methylthionine chloride in high aqueous dilutions detoxifies blood serum. This may offer some hope eventually for therapeutic trial of these substances.

ABSTRACT OF DISCUSSION

Dr. Isadore Rosen, New York: I am indebted to Dr. Pels and Dr. Macht for their examination of a large series of specimens from our clinic and for their report on their findings. I have prepared two slides to show the lipid studies for patients reported as toxic by Dr. Pels and Dr. Macht. One of them, Mr. F., aged 55, whose serum was reported as very toxic, showed on first examination an extremely low total cholesterol with an extremely high percentage of free cholesterol. Under treatment, which included arsenic in various forms and bismuth intramuscularly, he improved rapidly clinically. Repeated examination of the blood revealed a gradual increase of his total cholesterol to normal and a decrease of the percentage of free cholesterol to that within the normal range. These results checked well with the negative findings of Dr. Pels and Dr. Macht.

In some of our other patients with pemphigus for whom the phytopharmacologic test was reported as toxic, we found a high total cholesterol, and in those in whom clinical improvement was obtained there was a decided reduction to normal.

Dr. Howard Fox, New York: I have been greatly interested in the work of Dr. Pels and Dr. Macht which promises to be of definite practical value. There is no pathognomonic clinical sign of pemphigus, and no laboratory test is of value unless that of the essayists proves to be such.

In my experience with 19 cases, mostly at Bellevue Hospital, the phytopharmacologic test has been helpful in differentiating pemphigus from other bullous conditions. Three of my cases were clinically erythema multiforme of the bullous type, all of which showed normal readings (from 70 to 78). Nine cases were undoubtedly pemphigus, from the clinical standpoint, most of the patients having died in the hospital. All gave toxic readings (from 50 to 56) with the exception of 1 man (reading of 73) who entered the hospital the day before he died. In 7 of my cases the diagnosis of pemphigus was in doubt, and all except 1 of these showed normal readings (75 to 86). The single exception was a curious

case presented before the New York Dermatological Society in which no one was able to make a definite diagnosis. The patient had an itchy dermatitis with vegetating lesions. His reading was 68, or just below normal. Another case was shown before this society as one for diagnosis. No one was willing to call the condition pemphigus. The patient was later treated by Dr. Wise, at which time the type of the eruption changed and was considered to be pemphigus. The patient made a complete recovery, which in the opinion of some would make the diagnosis of pemphigus doubtful.

Dr. Paul A. O'Leary, Rochester, Minn.: The phytopharmacologic test has been of definite aid to us in the diagnosis when an early case of pemphigus was suspected. We have sent Dr. Pels 36 specimens of blood drawn from persons with pemphigus, erythema multiforme and pellagra. In the group with pemphigus the test and our clinical diagnosis were in accord in 70 per cent of the cases. Some of the discrepancy may be attributed to the fact mentioned by Dr. Pels that when the patient is moribund from pemphigus, the report is apt to be nontoxic. The three pellagrins all gave highly toxic readings. We have been observing for several years a patient of Dr. A. M. Davidson of Winnipeg, who presented bullous lesions of the mouth and genitalia. The diagnosis of pemphigus seemed warranted, and the Pels test confirmed this impression. A remission developed twice, and on each occasion the test was reported within normal limits, but when the bullae recurred the test was reported as toxic.

We feel as Dr. Pels and Dr. Macht do, that the test is by no means infallible, and that it has definite limitations, although at the same time it is of aid in arriving at a diagnosis in an early case of pemphigus.

Dr. William H. Guy, Pittsburgh: I wish to express my appreciation to Dr. Pels for continuing this work which gives great aid in the conditions which are confusing. Our batting average, I think, runs a little higher than cited by Dr. O'Leary. It seems to me that the interpretation of this test as a nonspecific test is of some importance, and that an examination should be made of extensive scalds and burns to determine if the plant growth-inhibiting toxin occurs as a result of extensive alteration in the skin independent of pemphigus.

Dr. Isaac R. Pels, Baltimore: We are always grateful to have notice taken of this test, because we feel that if we had not had help throughout the country we would not have been able to go on with the large number of specimens which were tested. The various speakers, Dr. Fox and Dr. O'Leary particularly, have stressed one thing that we tried to bring out in the paper, namely, that this test, if done as a nonspecific test, should make us more guarded in our clinical diagnoses. We would not be so likely to accept a diagnosis of pemphigus because a patient has bullae and is very ill. Repeated tests are desirable as a check-up. In cases which prove not to be pemphigus, because the patient does not die, repeated tests should be of some assistance. We have seen a number of instances in which a diagnosis of pemphigus was suggested, and in two particularly the patients remained well. One of these was very ill—a woman whom Dr. Fox and others saw. She left the hospital and did not die, whereas next door to her was a woman who died within a few weeks of typical pemphigus vulgaris. Both patients gave toxic readings. Where to allocate these cases is still a problem, and the question is: Is there a disease which is not pemphigus but which is equally severe?

Dr. Guy's statements about burns interested me. We procured blood from such cases on two occasions, and, as I recall, the reading was not toxic, but, of course, we cannot make any comment on so few.

Dr. Rosen's comments and studies are interesting because they concern something which Dr. Macht has been interested in. Dr. Macht wishes to understand what this toxicity consists of. He is particularly concerned with the pharmacologic aspect, and it is hoped that he will give us some definite information about it some day.

We did not mention results in leprosy. A number of cases of leprosy have been studied and in the main gave highly toxic readings, averaging 47 per cent. We have had specimens both from this country and from abroad. This toxicity interested us particularly because of the fact that we sometimes have to consider leprosy when we get a positive blood test. This may lead to some definite diagnostic information in the future.

MULTIPLE BENIGN TUMOR-LIKE NEW GROWTHS OF THE SCHWENINGER-BUZZI TYPE

REPORT OF A CASE

NORMAN TOBIAS, M.D.
ST. LOUIS

The primary macular atrophies are of sufficient rarity and interest to warrant the report of a classic case of the Schweninger-Buzzi type of cicatricial atrophy. The interesting feature is the linear distribution of the lesions on the shoulders and upper part of the back, a fact which coincides with Schweninger and Buzzi's original description.[1]

REPORT OF CASE

History.—J. B., a white woman, married, aged 26, was first seen in June, 1929, at St. Mary's Dispensary where she sought treatment for "spots" on her body.

The family history was unimportant. There was no history of any cutaneous diseases in the parents or relatives.

The patient had mumps and tonsillitis in childhood, typhoid at 12 years of age and lobar pneumonia three times. She also gave a history of eleven induced miscarriages. She said that she never had a venereal disease or any of the symptoms of one. There was no evidence of tuberculosis or syphilis.

The present eruption began as a half dozen pink macules on the forearms resembling "mosquito bites." At no time did they itch, scale or become purulent. In about two weeks following the presence of the eruption, scar formation developed with ballooning. About four or five new lesions appeared each year. At the time this article was written the patient had eighty-four lesions on the body.

Physical Examination.—The patient was a well nourished and developed white woman, a brunette. The hair was chestnut, and normal in color and distribution. No lesions were present on the face. The teeth and mucous membranes of the mouth were normal. However, the palate was highly arched, and the tonsils were hypertrophic. Examination of the neck revealed a palpable thyroid.

The extensor surfaces of the shoulders, arms, forearms and upper half of the back and chest and the sides of the neck were covered with a more or less symmetrical eruption of numerous oval and round, slate-colored, bladder-like smooth scars. Many of these resembled tumors until one palpated them and found that they were soft and could be invaginated with the little finger about a centimeter, only to puff out again when pressure was released. Extension of the underlying muscles and tension on the skin decreased the ballooning effect. The largest scars

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From the Department of Dermatology, St. Louis University.

1. Schweninger, E., and Buzzi, S.: Internationaler Atlas seltener Hautkrankheiten, Leipzig, Leopold Voss, 1891, vol. 5, plate 15: "Several exist along the spine while on each side they become fewer in number and have a linear arrangement according to the natural folds of the skin."

were 2 cm. in size and the smallest ones varied from 0.5 to 1 cm. Dilated capillaries were present over a few of the older lesions on the back. The more recent lesions were violaceous and showed no ballooning. An interesting observation was the linear arrangement of the scars over the clavicular and scapular regions.

On the extensor surface of the right arm, there was a large tattoo which was free from scars. Otherwise no pigmentary lesions were present.

Course.—While the patient was under observation for six months, three new lesions developed on the right forearm. The older lesions showed no sign of retrogression. During this peroid the patient gained 12 pounds (5.4 Kg.) in weight. It seemed to increase the prominence of the lesions on the back and extensor surfaces of the extremities.

Because of the history of multiple miscarriages, the patient was referred to the gynecologic clinic and a diagnosis of hypertrophic endometritis was made. Dilation and curettage were performed with an uneventful recovery.

Laboratory Data.—The Kahn and Wassermann reactions were negative. A provocative dose of 0.3 Gm. of arsphenamine failed to affect the blood. Blood cultures were negative. The blood count showed 4,200,000 red cells and 8,700 white cells, with a normal differential count. The urine was normal. The basal metabolic rate was plus 15; the blood sugar, 102 mg. per hundred cubic centimeters, and the nonprotein nitrogen, 24 mg.

Biopsy.—A section was taken from the left forearm. The entire epidermis was thinned out with flattening of the papillae and absence of the stratum germinativum. The section stained weakly with hematoxylin and eosin.

The upper part of the corium was edematous with small scattered streaks of round cell infiltration, especially around the lymph and blood vessels. No coil or sebaceous glands were present. The collagen bundles were thinned out and took a faint stain. No elastic tissue fibers could be seen in the section stained with Weigert's solution.

The lower part of the corium showed several areas of lymphocytic infiltration. The collagen bundles were normal in size and amount but appeared swollen. The elastic tissue fibers appeared thin and shredded.

EXCESSIVE SOLAR AND PHOTOTHERAPEUTIC IRRADIATION

A CAUSATIVE FACTOR IN CERTAIN DISEASES OF THE SKIN

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The use of heliotherapy originated with that sage of Kos and high priest of medicine, Hippocrates. A great temple known as the Aesculapion was built on the slope of a mountain. It faced south so as to receive the maximum of sunlight. The temple was dedicated to Aesculapius, and in this institution sun bathing was indulged in. Ancient Egypt appreciated the power of sunlight, and in the fourth dynasty, Ra, the sun, became the "king of the gods." In the eighteenth dynasty, Aton became predominant, which was an entirely different conception of the sun than Ra. Aton, according to Petrie,[1] was the beneficent sun; its beams imparted life and power to the reigning king. The Romans also made the sun an object of adoration. Cicero mentioned the sun bath, and during his time solaria were popular. Herodotus and Antyllus recommended sun bathing for diseases of the skin. Heliotherapy remained dormant throughout the dark ages.

Faure, in 1777, utilized heliotherapy in the treatment of ulcers; Ollier and Poncet, in 1840, were the pioneers in its use in tuberculous arthritis, but it remained for Niels Ryberg Finsen to prove himself the father of modern phototherapy.

In the past few years exposure of the body to the sun and to the myriad ultraviolet ray machines without medical advice or supervision has attained such popularity as to warrant a dispassionate array of facts dealing with the dangers thereof. These dangers are not, of course, unknown to an audience of fellow dermatologists but they are unknown to the layman and to the general practitioner. Despite a growing literature, the subject has not received, even from dermatologists, the attention its importance deserves. There exists a large group of dermatoses whose relationship to excessive actinic exposure cannot be attributed entirely to coincidence. The more important of these will be considered in this paper.

Read before the Section on Dermatology and Syphilology at the Eighty-Fourth Annual Session of the American Medical Association, Milwaukee, June 16, 1933.

1. Petrie, William: The Religion of Ancient Egypt, New York, Bloch Publishing Company, 1906.

EPITHELIOMA

Unna, as early as 1896, described "sailor's skin," which he named "Seemanshaut," but it was Dubreuilh [2] who first recognized, in 1907, the possible etiologic rôle that excessive solar burns played in the causation of epithelioma. Since Dubreuilh's pioneer work there have been a considerable number of articles corroborating his findings, and the evidence gathered from these writings in favor of Dubreuilh's hypothesis is convincing, especially if one applies the elementary law of common sense in weighing it. What are the facts favoring this hypothesis? In all strictness, they are circumstantial but nevertheless important. A synopsis of the evidence follows:

The natural inhabitants of tropical zones are dark-skinned or negroid. Might not this be due to a beneficent act of Mother Nature to protect the skin from the sun? It is well known that cancer of the skin is rare in the colored race; this has been attested time and again by clinical observation, as has also the fact that keratoses and epitheliomas are much more common in blonds and in persons with red hair than in decided brunettes. Cancer of the skin is rarely seen among dark Italians. McCoy [3] found that in his private practice 62 per cent of the cases of cancer of the skin occurred in blonds, 31 per cent in persons with auburn hair and only 7 per cent in dark-skinned persons. Ninety-three and five-tenths per cent of these patients were farmers or were engaged in outdoor vocations. Corlett, in 1915, commented on the great frequency of cancer of the face, neck and hands in agricultural laborers. Dubreuilh made similar observations in the rural districts around Bordeaux, France. Most of the farmers with cancer came from a region in southwest France where the soil consisted of a peculiar white chalk, which increased ultraviolet irradiation by reflection. McCoy,[3] in this country, compared a district with soil of white clay with one with soil of reddish-yellow clay; the inhabitants of the latter had fewer cancers and keratoses than those with the same vocations living in the district with white clay soil. The same author, during the summer of 1918, noted a tremendously increased number of men suffering from solar burns in a camp situated on a soil of white clay.

Molesworth [4] reported a marked increase in the incidence of cancer of the skin in Australia over that in England. The light-skinned Scotch-

2. Dubreuilh, W.: Epithéliomatose d'origine solaire, Ann. de dermat. et syph. **8**:387, 1907.

3. McCoy, James N.: The Solar Keratosis and Cutaneous Cancer, Arch. Dermat. & Syph. **1**:175 (Feb.) 1920.

4. Molesworth, E. H.: Rodent Ulcer, M. J. Australia **1**:878, 1927.

Irish inhabitants were particularly susceptible. Lawrence [5] also commented on the great frequency of cancer of the skin in Australia. He ascribed this incidence to the low humidity of that continent and to the great amount of sunshine, with a consequent unusually high content of solar ultraviolet rays. Lawrence observed 1,769 cancers of the skin among 20,000 patients with cutaneous diseases. Both authors commented on the fact that the number of days of sunshine in England is half that in Australia, and that the incidence of cancer of the skin is also halved. Findlay [6] cited the interesting observation of Young and Russell that they found an excess of facial cancer in fishermen, bargemen and lightermen, while farmers, agricultural laborers and gardeners suffered mostly from cancer of the back of the hand. Larabi [7] commented on the fact that 90 per cent of cutaneous epitheliomas occur on the exposed parts of the body, especially the face, and that even there they are more common on the areas not covered with hair.

Animal experimentation has proved the incidence of cancer of the skin after prolonged ultraviolet irradiation. Putschar and Holtz [8] exposed rats to irradiation from the mercury vapor arc in quartz (150 volts; from 2 to 4 amperes) at a distance of 60 cm., the time being increased from two minutes at first to twenty-four hours after thirteen days. By the twenty-eighth week many epitheliomas appeared, of basal and mixed types. A number of the rats demonstrated cutaneous horns. After from thirty-one to forty-seven weeks, metastases occurred in three. Herlitz, Jundell and Wahlgren [9] exposed two groups of mice to irradiation from the mercury vapor arc quartz; a third group was used as a control, and was not exposed. After thirty weeks, in the irradiated mice there invariably developed epidermal neoplasms, usually carcinomatous but sometimes more closely resembling some form of sarcoma. Instances of metastases were observed. The control series remained normal, showing no tumor formation.

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5. Lawrence, Herman: The Relative Low Humidity of the Atmosphere and Much Sunshine as a Causal Factor for the Great Prevalence of Skin Cancer in Australia, M. J. Australia **2**:403 (Sept. 29) 1928.

6. Findlay, G. M.: Ultra-Violet Light and Skin Cancer, Lancet **2**:1070 (Nov. 24) 1928.

7. Larabi, Mahmond: L'action cancerigène de la lumière solaire, Thèse de Paris, 1932.

8. Putschar, W., and Holtz, F.: Erzeugung von Hautkrebsen bei Ratten durch langdauernde Ultraviolettbestrahlung, Ztschr. f. Krebsforsch. **33**:219, 1930.

9. Herlitz, C. W.; Jundell, I., and Wahlgren, F.: Malignant Neoplasms Caused by Ultra-Violet Irradiation of White Mice, Acta pædiat. **10**:321 (March 15) 1931.

DISSEMINATE LUPUS ERYTHEMATOSUS

Disseminate lupus erythematosus is a new danger from sun bathing which has recenty been recognized. At the Atlantic Dermatological Conference held in New York on Dec. 16, 1925, I presented [10] a man, aged 54, with typical discoid lupus erythematosus of the face only. The patient inadvertently received a single treatment with the air-cooled mercury vapor arc in quartz, the chest and arms being left unprotected. Marked erythema ensued, which immediately assumed the characteristics of severe disseminate lupus erythematosus, covering the chest and arms and soon spreading to the hands. Oliver, in discussing the case, stated that he had observed a number of cases originating from sunburn.

At the meeting of the New York Dermatological Society on Jan. 26, 1932, I presented [11] a second case, in a man, aged 47, who in September, 1931, suffered a severe sunburn, which confined him to his room for a week. His face and forearms were a mass of bullae. Immediately thereafter sharply outlined violaceous red plaques appeared on the face, in the typical "butterfly" area. On the arms and the backs of the fingers were bluish-red spots. The eruption had been present for six months and consisted of large, red, sharply outlined plaques on the face in the typical location, with prominent, patulous follicular openings and some scaling. The forearms, the backs of the hands and the fingers were greatly involved.

A third case occurred in a woman, aged 27, in splendid health. On May 30, 1932, she suffered a severe sunburn, which left a persistent, slightly scaly red patch on the bridge of her nose; the patch was still present a month later, when a second sunburn increased its size immediately. The patch persisted, and after a third prolonged exposure to the sun a month later (two months after its first appearance) typical generalized acute lupus erythematosus developed all over the face, of which some remains were present a year later, after several months of aurotherapy.

At the Atlantic Dermatological Conference held in Philadelphia on Nov. 11, 1932, Greenbaum [12] exhibited a girl, aged 4, with erythematous, scaly patches over the nose and both cheeks, with dissemination to the hands, which originated about three years previously after a sunburn at the seashore and were greatly aggravated by exposure to an ultraviolet ray lamp for six months. The child also had granuloma annulare.

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10. Bechet, P. E.: Lupus Erythematosus Disseminatus, with Extension of the Disease After Exposure to Actinic Light, Arch. Dermat. & Syph. **13**:701 (May) 1926.

11. Bechet, P. E.: Acute Disseminate Lupus Erythematosus Following Sunburn, Arch. Dermat. & Syph. **26**:538 (Sept.) 1932.

12. Greenbaum, S. S.: Lupus Erythematosus and Granuloma Annulare, Arch. Dermat. & Syph. **27**:709 (April) 1933.

Rasch [13] grouped ninety-four cases of lupus erythematosus in relation to date of incidence of the disease. Fifty-four, or over half, began in the months from March to June, when the actinic rays of the sun are most irritating in Copenhagen. He had seen a number of cases of the disease in which parts protected from light were entirely free, with a sharp line of demarcation between the exposed and the affected parts. Rasch maintained that "light is, on the whole, the most important external factor of this disease." MacKee [14] warned against undue exposure to ultraviolet rays, either natural or artificial, in cases of discoid lupus erythematosus, because of the danger of inducing dissemination.

In a paper of this kind I do not believe it proper to discuss those diseases due to excessive photosensitization apparently of endogenous origin, such as hydroa aestivale, in which hematoporphyrin is found fairly frequently in the urine, and xeroderma pigmentosum, in which hematoporphyrin is seldom if ever found and in which consanguinity and familial tendencies seem to bring on an insufficient resistance of the skin to actinic rays.

The rôle of hematoporphyrin in photosensitization is most interesting; the condition can be artificially induced, a fact well demonstrated by Meyer-Betz [15] in an experiment on himself, in which he suffered severe reactions to actinic rays after the injection of this pigment. Hausmann [16] injected hematoporphyrin into white mice, which promptly died, with characteristic symptoms, on exposure to light. Control animals kept in the dark showed no symptoms. Black mice could not be sensitized. Urticaria caused by sunlight has been reported by Ochs,[17] Duke,[18] Beinhauer,[19] Ward [20] and others. Ayres [21] reported five cases of chronic cheilitis due entirely to solar rays.

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13. Rasch, C.: Some Historical and Clinical Remarks on the Effect of Light on the Skin and Skin Cancer, Proc. Roy. Soc. Med. (Sect. Dermat.) **20**:1 (Nov.) 1926.

14. MacKee, G. M.: Ultraviolet Therapy in Dermatology, J. A. M. A. **98**: 1553 (April 30) 1932.

15. Meyer-Betz, F.: Deutsches Arch. f. klin. Med. **112**:476, 1913.

16. Hausmann: Biochem. Ztschr. **20**:276, 1910.

17. Ochs, B. F.: Case of Urticaria Caused by the Sun's Rays, M. Rec. **78**: 193, 1910.

18. Duke, W. W.: Urticaria Caused by Light, J. A. M. A. **80**:1835 (June 23) 1923.

19. Beinhauer, L. G.: Urticaria Solaris, Arch. Dermat. & Syph. **12**:1 (July) 1925.

20. Ward, S. B.: Erythema and Urticaria with a Condition Resembling Angioneurotic Edema, Caused by Exposure to Sun's Rays, New York M. J. **81**: 742, 1905.

21. Ayres, Samuel, Jr.: Chronic Actinic Cheilitis, J. A. M. A. **81**:1183 (Oct. 6) 1923.

Among other dermatoses caused by solar actinic rays are the chronic polymorphic light eruptions, the so-called war melanosis described by Riehl,[22] and Jadassohn's [23] cutis rhomboidalis nuchae.

Erythema multiforme, psoriasis and syphilis are occasionally increased by severe sunburn. I have seen a patch of psoriasis on the shoulder divided in half by the strap of a bathing suit. Herpes facialis due to solar irritation is not uncommon. For years I have had recurrent attacks of herpes labialis after severe sunburn but am entirely free during the winter months.

Ultraviolet ray lamps are not entirely free from danger, as is commonly supposed. MacCormack and McCrea [24] reported the development of severe toxic dermatitis actinica in a man, aged 72, following an exposure to an ultraviolet ray lamp for one hour and ten minutes. The patient almost died. The eruption was very severe even a month later. The back was greatly involved, although it had not been exposed to the light. Humphris [25] observed a fatal case in a woman, aged 48; death supervened twelve days after exposure to a "sun lamp." She had severe burns on the left leg and the lower part of the back. Fever, diarrhea, hematemesis and hematuria developed a few days after the burn. Postmortem examination revealed gastric and duodenal ulceration as the result of the severe burn.

CONCLUSION

The fact that excessive exposure to actinic rays, either natural or mechanical, is an important etiologic factor in certain diseases of the skin is supported by the evidence submitted.

While all dermatologists know this, they have not emphasized it sufficiently, with the result that there exists complete ignorance among laymen as to the ill effects of prolonged actinic exposure. While such effects are admittedly infrequent, they are sufficiently important to be reported again here.

ABSTRACT OF DISCUSSION

DR. ELMER B. TAUBER, Cincinnati: Charcot was the first to show that sunburn was due to rays of short wavelengths. Finsen showed that light caused prolonged dilatation of blood vessels, and his assistant, Bangs, demonstrated a marked accompanying leukocytosis. Pigmentation and tanning are nature's armor to pre-

22. Riehl: Ueber eine eigenartige Melanose, Wien. klin. Wchnschr. **30**:780, 1917.

23. Jadassohn: Cutis rhomboidalis nucha mit colloider Degeneration, Zentralbl. f. Haut- u. Geschlechtskr. **17**:272, 1925.

24. MacCormack, H., and McCrea, H. M.: Severe Dermatitis Following Ultra-Violet Light, Brit. M. J. **1**:693 (April 11) 1925.

25. Humphris, F. H.: Artificial Sunlight and Its Therapeutic Uses, New York, Oxford University Press, ed. 5, 1928, p. 133.

vent the penetration of rays of short wavelengths which are harmful, and this protection is in direct proportion to the intensity of the light. James Weir stated that violet rays are absolutely necessary in the building of a normal body. There are three effects: (1) nervous, stimulating the vasomotor nerves and resulting in dilatation of blood vessels; (2) chemical, resulting in alteration of the blood-producing cells and plasma, and (3) physiologic, stimulating cell growth and the formation of new tissue.

There is no doubt that epithelioma occurs in farmers on the exposed surfaces of the body where the direct sunlight acts. Cases of disseminate lupus erythematosus caused by the action of sunlight have been reported, as well as cases of herpes facialis and actinic dermatitis. Gron reported violent dermatitis following slight exposure to sunlight. Brocq reported hydroa vacciniforme caused by sunlight.

I am sure that excessive solar and phototherapeutic rays have a decided action on the skin. Unfortunately, owing to the high-pressure salesmanship of manufacturers of various lights, the lay public has been made to believe that sunlight and "sun lamps" are, to paraphrase Kipling, "the light that never fails." This is far from the truth, as can easily be demonstrated.

The severe action of sunlight or phototherapeutic ultraviolet rays is well known. Burned living tissue is definitely toxic. This can be proved by burning living tissue and placing it in the peritoneal cavity of a rabbit; severe toxicity results. Burning dead tissue and inserting it in the peritoneal cavity produces no such effect. The cause is probably the production of an albuminate, a peptone or a proteose that is akin to snake venom; so in a milder degree one suffers in a similar way from excessive sunburn or erythema over large surfaces due to ultraviolet irradiation.

BLOOD LIPIDS IN XANTHOMA

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In this report we shall record studies of the blood lipids in three cases of xanthoma tuberosum and in five cases of xanthoma palpebrarum or xanthelasma. This work was incited by the report of Schaaf and Werner [1] on the imbalance of the lipid constituents of the blood that they found in the aforementioned disorders.

At this point we should state that we follow Bloch [2] in regarding xanthoma multiplex and xanthelasma as clinically dissimilar representatives of the same disease. This may not be current American opinion; Wile, for one, regards them as entirely different diseases. In differing from that author, we refer to the reasons given by Bloch, which are readily available and need not be repeated here, and add that Pollitzer's [3] pathologic study of xanthelasma (this appears to be the basis for the opinion that xanthelasma is an entirely different disease from xanthoma) is criticized by Gans [4] for the reason that the degeneration of the orbicularis palpebrarum described by Pollitzer as fundamental for the pathogenesis of xanthelasma is a fairly frequent expression of a simple senile degeneration.

Before recording our findings we wish briefly to review the present status of the pathogenesis of xanthoma. Until the studies of Wile, Eckstein and Curtis [5] the pathogenicity of xanthoma was practically universally accepted as being based on a circulating hypercholesteremia and deposition of that substance at various sites, probably as the result of trauma, infection or other alterations in the tissue. The fact that about 30 per cent of the cases of xanthoma showed no increased circulating cholesterol was either passed over or ascribed to purely hypothetic affinities of the tissues for cholesterol (Siemens' cholesterphilia).

Wile and his collaborators showed definitely, however, that the conception of the cause of xanthomatous deposits obtaining at the time of

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1. Schaaf, F., and Werner, A. J.: Arch. f. Dermat. u. Syph. **162**:217, 1930.
2. Bloch, B.: Brit. J. Dermat. **43**:61 (Feb.) 1931.
3. Pollitzer, S.: J. Cutan. Dis. **28**:633 (Dec.) 1910.
4. Gans, Oscar: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, vol. 1, p. 145.
5. Wile, U. J.; Eckstein, H. C., and Curtis, A. C.: Lipid Studies in Xanthoma, Arch. Dermat. & Syph. **19**:35 (Jan.) 1929.

their studies was faulty and unacceptable. These workers reported three cases of xanthoma multiplex, in two of which there were normal blood cholesterol and total lipid values, and in the other, that of a patient with diabetes, a greatly increased lipemia and hypercholesteremia, but not a corresponding increase in the circulating cholesterol. Furthermore, analysis of xanthoma tumors revealed that the amount of cholesterol present was from 1.5 to 2 per cent of the total mass and only about 16 per cent of the total amount of lipids in xanthomatous tissue. Wile, Eckstein and Curtis [6] later reported further studies corroborating their original observations.

The unsatisfactory state in which the question was left challenged further investigation, and this was undertaken by Schaaf and Werner.[1] These workers reported analyses of the entire lipid fractions present in the blood in three cases of xanthoma tuberosum, one case of xanthoma bulbi and four cases of xanthelasma. Five of their cases were analyzed by a single determination after an appropriate diet and a twelve hour fast; three were studied by means of a cholesterol tolerance test. In every case a disturbance of the normal ratio of the lipid constituents of the blood was found. Schaaf and Werner concluded that two kinds of disturbances in the lipid fractions are responsible for the formation of xanthomas. First, this may consist in an alteration in the ratio of free to bound cholesterol, and second, there may be an abnormal change in the proportions of the neutral fats, phosphatides and total cholesterol. The authors regard this imbalance as of fundamental importance in the pathogenesis of xanthoma. The physicochemical investigation of Spranger [7] on lipid emulsions is referred to by Schaaf and Werner as basic for the conclusions at which they arrived; namely, that an imbalance of the lipid constituents of the blood produces an unstable emulsion which favors the deposition of the blood lipids under local changes in the tissues. Xanthoma, therefore, according to these investigators, is the expression of a disturbance of the fat metabolism leading to an imbalance of circulating lipids. The unstable emulsion which is represented by the blood is deemulsified under circumstances which would not, presumably, influence a normal blood emulsion, and the resulting deposition of blood fats results in the formation of xanthomas. These authors, likewise, presume that the primary disturbance which underlies the disordered fat metabolism is seated in the liver.

Schaaf [8] later reported a case of Schüller-Christian disease with xanthelasma and diabetes insipidus in which two fat tolerance tests were made. This case likewise revealed a disturbance of the fat metabolism,

6. Wile, U. J.; Eckstein, H. C., and Curtis, A. C.: Lipid Studies in Xanthoma: Further Contribution, Arch. Dermat. & Syph. **20**:489 (Oct.) 1929.

7. Spranger, W.: Biochem. Ztschr. **208**:164, 1929.

8. Schaaf, F.: Arch. f. Dermat. u. Syph. **163**:58, 1931.

but not in the same direction as those first reported by that author. In that case, Schaaf found an abnormal behavior to the cholesterol tolerance test rather than a pronounced abnormality in the ratio of the various blood lipids. The case indicated that the disturbed fat metabolism underlying the disease might be detected only by a fat tolerance test.

A readily available résumé of the investigations of Schaaf and Werner was given by Bloch.[2] We wish also to refer to an exhaustive review by Schaaf [9] of the whole subject of lipid metabolism.

PREPARATION OF PATIENTS

For the twenty-four hours preceding the removal of blood for analysis, the patients were instructed to abstain from all fats, oils, cream, butter, eggs and meats (including viscera and organs). A small amount of skimmed milk was allowed. The blood was removed after at least a twelve hour fast. The patients who were given a cholesterol tolerance test remained on the diet until the test was completed.

For the cholesterol tolerance tests a sample of blood was taken during fasting; the subject was then given 5 Gm. of cholesterol in 100 Gm. of olive oil made into mayonnaise with one egg and lemon juice. It was eaten with a small boiled potato. Blood was withdrawn four, eight and twenty-four hours after the test meal (in two cases the last sample was unobtainable).

METHODS OF ANALYSIS

Ordinarily, in a paper of this type the mere reference to the methods of analysis used is sufficient. Since, however, Bloch [2] and his associates have raised the point as to the proper method of determining the various lipid constituents, it is necessary to discuss briefly the procedures used by us. It appeared to us to be highly important to obtain a uniform extract of the lipids containing all the lipid constituents we were to determine. Accordingly, Bloor's method [10] of preparing the ether-alcohol extract was used in all cases. The procedure simply stated is as follows: A 5 cc. sample of serum was pipetted slowly into a 100 cc. volumetric flask containing 75 cc. of a 3:1 mixture of alcohol and ether. This was then brought to the boiling point and the mixture allowed to stand for twenty-four hours before being made up to volume and filtered. We used 10 or 20 cc. aliquots of this extract for the determinations. For the determination of cholesterol and cholesterol esters, Bloor's colorimetric methods [11] were used. All evaporations were done in a water bath the temperature of which never exceeded 80 C., and the colors developed, on the addition of the acetic anhydride and concentrated sulphuric acid, were always a pure green and compared identically in shade with the color of the cholesterol standard. In choosing Bloor's methods of analysis in preference to others, we were guided by the statement of Peters and Van Slyke [12] that "even if Bloor's methods do yield somewhat excessive values for cholesterol at times, their adaptability to his system for the quantitation and fractionation of all the blood lipids gives them a peculiar value." For the determination of the

9. Schaaf, F.: Zentralbl. f. Haut- u. Geschlechtskr. **35**:1 and 193, 1931.

10. Bloor, W. R.: The Determination of Small Amounts of Lipid in Blood Plasma, J. Biol. Chem. **77**:53, 1928.

11. Bloor, W. R., and Knudson, A.: The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, J. Biol. Chem. **27**:107, 1916.

12. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 1, p. 9; vol. 2, p. 490.

phosphatide fraction, a 20 cc. aliquot was evaporated and ashed, the resulting inorganic phosphate being determined by Fiske and Subbarow's[13] colorimetric method. Total lipids were determined by evaporating a 20 cc. aliquot just to dryness, then dissolving in purified petroleum benzine and filtering through a fat-free filter paper into a weighed platinum crucible. The purified petroleum benzine was evaporated and dried to constant weight at 75 C., and the residue was weighed on a microbalance, according to the technic of Fowweather.[14] It was our belief that, in this determination especially, a gravimetric determination of the absolute amount of lipid material in the alcohol-ether extract was a more reliable value than the results obtained by oxidation or other methods. Since the determinations of total lipids, phosphatides and cholesterol were all made on the alcohol-ether extract, the main source of error would be in the preparation of this extract and not in the relative distribution of the various fractions of the total lipid content, which is the important consideration in this investigation, according to Bloch[2] and his associates. That is, the disturbance in the normal distribution of phosphatides, neutral fats and soaps, free cholesterol and cholesterol esters rather than the absolute quantities of these constituents is the deciding factor as to whether or not a lipid-water emulsion will become unstable.

REPORT OF CASES

CASE 1.—*Xanthoma Multiplex.*—A. R., a Negro, aged 47, first noticed small hard nodules on the elbows and knees four years before he was admitted to Hermann Hospital. They caused him no discomfort except when struck or pinched. This induced pain.

The lesions were typical of xanthoma tuberosum, being present over the olecranons and patellae in the form of walnut-sized, chamois-colored nodules, on the buttocks as numerous pea-sized papules and in each palm as linear streaks.

His general health and functions were normal, except for occasional distention and pain after meals. His height was 5 feet and 10½ inches (179 cm.), and his weight, 184 pounds (83.5 Kg.). Physical examination revealed no conspicuous abnormalities. A stereoroentgenogram of the skull revealed nothing abnormal. Laboratory examinations showed a negative Wassermann reaction and a normal hemanalysis. The urine contained a very faint trace of albumin and a trace of sugar. The blood sugar was 87 mg., the nonprotein nitrogen, 42.8 mg., and the creatinine, 1.8 mg. per hundred cubic centimeters of blood. Further examinations to determine the significance of the urinary sugar were not made because the patient was forced to leave the hospital on completion of the studies of the lipids. In view of the low blood sugar he probably did not have diabetes mellitus.

One of the large nodules on the right elbow was removed for histologic and chemical studies. The histologic changes were typical of xanthoma tuberosum. A cholesterol tolerance test was made at the hospital.

CASE 2.—*Xanthoma Multiplex.*—The blood from this case was obtained through Dr. H. R. Foerster and Dr. R. L. McIntosh of the department of dermatology, the University of Wisconsin. It was shipped to us by air mail in a sterile container.

The following particulars of the case are transcribed verbatim from the report given us by Dr. McIntosh.

"R. B., a white male aged 52, has always lived in Wisconsin and always been a farmer. His past medical history is unimportant. However, about five years ago

13. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

14. Fowweather, F. S.: The Determination of the Amount and the Composition of the Fat Faeces, Brit. J. Exper. Path. **7**:7, 1926.

he noticed that there were some smooth, yellowish nodules on the skin behind his ears. They seemed to enlarge fairly rapidly and at the same time new and similar lesions appeared on his neck, forehead, shoulders, arms, and face, the ones on his eyelids being especially annoying. The other lesions gave rise to no syptoms except that after being in the hot sun, they seemed to 'draw' and were tender. He did not consider it necessary to do anything about his condition until his eyes began to give him trouble and his throat began to 'thicken.' He then consulted his physician and was sent to the Wisconsin General Hospital on September 26, 1932.

"Physical examination revealed a fairly muscular man weighing 135 pounds who had, in addition to his widespread xanthoma, the following physical findings: (1) A marked ectropion of all four eyelids with attendant hyperlacrimation. (2) A very loud inspiratory and expiratory rattle in his throat and a peculiar roughened harsh voice. The neck was so thickened by the masses of xanthoma that normal movement was greatly impaired. (3) The lungs were essentially normal. (4) The heart was slightly enlarged to the left and there were several murmurs heard. There was a presystolic murmur heard at the aortic area and in the third left interspace, while systolic murmurs were heard at the apex and at the mitral area. The blood pressure was 210 over 140, and there was a positive centrifugal venous pulse. (5) The liver was 3 fingerbreadths below the costal margin.

"Laboratory examinations revealed that the urine contained 0.005% albumin, many mucous shreds, one or two coarsely granular casts and six to eight hyaline casts per h.p.f. and about ten wbc per h.p.f. There was no sugar in the urine. The blood counts showed 55% Hb; 3,560,000 rbc; 6,900 wbc with 64% pmn and 36% lymphocytes. The blood contained 82 mg. sugar, 52 mg. nonprotein nitrogen, 1.6 mg. creatinine and 168.6 mg. cholesterol. The blood Wassermann was negative. A stereoroentgenogram of the skull showed no abnormality in the bones, but the pineal gland was calcified and there were some granular deposits above and lateral to it which were considered as being in the choroid plexuses of the lateral ventricles. The sella was small and showed no sign of erosion.

"He was placed on a fat-free diet and returned to his home. I saw him last week, and his general condition is about the same, except that all of the xanthomatous deposits are smaller and more dry. His voice has improved, but he has lost five more pounds in weight. The laboratory findings are essentially as recorded."

CASE 3.—*Xanthomatosis.*—The blood from this patient was furnished by Dr. Toulmin Gaines, Mobile, Ala. It was collected and shipped in the same manner as in the preceding case. Dr. Gaines made this case the basis of a paper presented at the 1932 meeting of the Southern Medical Association. The paper appeared in the *Southern Medical Journal* (**26**:489 [June] 1933). Our notes were obtained from a copy of this paper.

The patient was a white man, aged 47, who presented large, doughy, disseminated nodules and purplish papules. He also had xanthelasma. The diagnosis was concurred in by Dr. A. Benson Cannon of New York, who saw the patient in consultation. The histology was that of xanthoma multiplex.

Roentgenographic studies showed an extensive destructive and absorptive process involving the joints and shafts of the bones of the hands, knees, shoulders and hips with no effort whatever at repair. A blood count gave a normal result. The determinations of nonprotein nitrogen, uric acid and creatinine in the blood gave average figures. There was a slight increase in the blood sugar. A sugar tolerance test showed some delay in the return to a normal blood sugar level, but was

probably of no especial significance. Urinalysis revealed no abnormalities. The Wassermann and Kahn reactions were negative. The basal metabolic rate was plus 13. A single specimen of blood was analyzed for its lipid constituents.

CASE 4.—*Xanthelasma.*—A woman, aged 54, presented a typical patch on each upper eyelid, which had been present for about six months.

She had a complete hysterectomy at 40 years of age. She was aware of high blood pressure for a number of years and had an apoplectic stroke in 1929. Otherwise, she had experienced no serious illnesses, especially no hepatic disease or jaundice.

Physical examination revealed a somewhat stout woman whose height was 5 feet and 3½ inches (161.2 cm.) and whose weight was 159 pounds (72.1 Kg.). There was a slight difficulty in speech. The cutaneous surface, with the exception of the lesions on the lids, showed no abnormalities. The liver was just palpable beneath the costal margin on deep inspiration. The heart was slightly enlarged; the sounds were regular and loud. The pulse was full and bounding. The blood pressure was 230 systolic and 130 diastolic. The urine showed an occasional granular cast, but no sugar. The case was a classic example of essential hypertension.

No histologic study was made. A cholesterol tolerance test was performed.

CASE 5.—*Xanthelasma.*—A man, aged 36, presented typical patches of xanthelasma on each lower eyelid which had been present for about three years. There was no other cutaneous disease. His height was 5 feet and 7 inches (170.2 cm.); his weight, 128 pounds (58.1 Kg.). Physical examination showed no visceral abnormalities. He had typhoid at 8 years of age; otherwise, he had never been sick. Urinalysis was negative for albumin and sugar. No other laboratory examinations were made.

A fat tolerance test was performed. This was carried through the eight hour period, but circumstances prevented the twenty-four hour analysis of lipids.

CASE 6.—*Xanthelasma.*—A woman, aged 54, presented typical patches of xanthelasma on each upper eyelid which had been present for a year. She had experienced no severe illness, except "blood poisoning" following an abortion in 1910. She had never been jaundiced or had any disease of the liver. The climacteric occurred at the age of 50. Her weight was 150 pounds (68 Kg.); her height, 5 feet and 2¼ inches (158.1 cm.). A general physical examination revealed no noteworthy abnormalities, except moderate obesity. No laboratory examinations were made.

A single estimation of the blood lipids was performed.

CASE 7.—*Xanthelasma.*—A woman, aged 45, had a typical lesion on each lower eyelid which had been present for about twelve years.

She had never been seriously ill. Except for constipation, her functions were normal. Her height was 5 feet and 5½ inches (166.3 cm.); her weight, 129 pounds (58.5 Kg.). No physical examination or laboratory studies were made.

A single estimation of blood lipids was performed.

CASE 8.—*Xanthelasma.*—A widow, aged 46, had patches of xanthelasma on the upper eyelids for about ten years. At the time of the test she was apparently in good health. Three years previously she had been examined by an internist for "rheumatism," but no significant abnormalities were detected. She weighed 147 pounds (66.7 Kg.), and her height was 5 feet and 3 inches (160 cm.). She gave the impression of being in good health. A routine physical examination and urinalysis revealed nothing significant.

CHEMICAL DATA

In each of our cases we have found a disturbance of the absolute and relative (or both) values of the blood lipids. On account of its bearing on the hypothesis of Schaaf and Werner, we lay more stress on percentage alterations than on absolute values of the lipid constituents. According to Bloch:[2]

The relative values of the individual components are of more importance than the absolute values. Consequently, a hypercholesterolemia does not mean very much of itself if the other lipid components are *proportionally* increased. On the other hand, if the cholesterol content is normal, or too low, there may be pathological conditions if the *ratio* of the free to the bound cholesterol is abnormal, or if the other constituents, e. g., the phosphatids, exhibit abnormal values. Any theory of the genesis of xanthoma which is based only on the absolute quantity of the total cholesterol content (hypercholesterolemia, hypocholesterolemia, normocholesterolemia) is incomplete and of doubtful value.

Our cases showed the following abnormal variations (table):

Distribution of Serum Lipid Fractions

Case	Diagnosis	Total Lipids, Mg.*	Percentage Distribution of Lipid Fractions: Neutral Fats, Soaps and Fatty Acids	Phosphatides	Cholesterol	Percentage of Cholesterol Esters to Total Cholesterol	Comment
1	Xanthoma multiplex	2,580	73.8	2.9	23.3	83.3	Fasting
		2,220	72.4	5.0	22.5	59.0	Fasting, 4 days later; before tolerance test
		2,240	77.0	3.6	19.4	63.8	4 hours after test meal
		2,330	75.3	3.1	21.4	66.8	8 hours after test meal
		2,220	73.0	3.3	23.6	68.0	24 hours after test meal
		1,780	57.5	22.7	19.8	61.3	2½ months later
		14,400†	43.4	31.3	25.4	87.8	Tissue composition about one month after first sample
2	Xanthoma multiplex	2,675	80.0	10.4	9.7	61.9	Fasting
3	Xanthoma multiplex	1,440	57.8	20.5	21.7	44.4	Fasting
4	Xanthoma palpebrarum	1,640	61.8	20.7	17.4	19.6	Fasting
		780	33.4	40.0	26.5	51.7	Fasting, 3 days later
		1,280	47.5	34.4	18.0	61.8	Fasting, next day, before test meal
		1,480	52.3	31.6	15.9	38.5	4 hours after test meal
		1,560	55.5	30.0	14.5	49.0	8 hours after test meal
		1,100	41.8	35.5	22.7	30.0	24 hours after test meal
5	Xanthoma palpebrarum	670	24.2	38.5	37.3	44.0	Fasting, before test meal
		860	43.7	31.1	25.2	62.3	4 hours after test meal
		600	29.7	37.4	32.9	45.7	8 hours after test meal
6	Xanthoma palpebrarum	1,540	52.6	19.5	27.9	70.0	Fasting
7	Xanthoma palpebrarum	880	23.2	44.3	32.6	25.5	Fasting
8	Xanthoma palpebrarum	720	16.0	47.2	36.8	35.8	Fasting, before test meal
		1,500	51.8	27.7	20.6	46.4	4 hours after test meal
		1,440	51.4	28.8	19.8	41.4	8 hours after test meal
		1,300	49.2	28.8	21.9	28.0	12 hours after test meal
	Normal	700	40-60	20-40	15-25	50-70	From Peters and Van Slyke[12]

* Milligrams per hundred cubic centimeters of serum.
† Milligrams per hundred grams of fresh tissue.

CASE 1.—There was a constant and pronounced hyperlipemia, which was manifested in the neutral fat, soap and fatty acid fraction and a marked reduction in the phosphatide fraction. Before and during the tolerance test the highest value obtained for the phosphatides was 112 mg. per hundred cubic centimeters (5 per cent of the total lipids against a normal of 30 per cent). On the other hand, in a single determination made four months later, after the patient had been on a low fat, cholesterol-poor diet and potassium iodide, the phosphatides had risen to 22.7 per cent of the total lipids. At that time there was a definite reduction in the size of the xanthomatous masses. During the tolerance test there was only a moderate increase in the total lipid content of the blood, and even a slight decrease in the total cholesterol figure. The percentage of total cholesterol to total lipids at all times approximated the normal, although the absolute amount of this constituent was from two to nearly three times the normal blood content. At the first analysis, 83 per cent of the total cholesterol was esterified, while during the tolerance test, the percentage of esterified cholesterol remained normal; it was normal also two and one-half months later.

CASE 2.—This case was characterized by a pronounced hyperlipemia constituted almost entirely of neutral fats, soaps and fatty acids. The phosphatide value was normal as to absolute quantity, but decidedly decreased in its percentual ratio to the total lipid content. There was a very moderate increase in the total cholesterol content, but estimated from the percentage standpoint, there was a decided diminution.

CASE 3.—In this instance there was hyperlipemia, but with a normal percentual ratio of the neutral fat, soap and fatty acid fraction. The cholesterol ester-free cholesterol ratio was diminished.

Case 4.—Except for one sample, there was hyperlipemia. The cholesterol percentage had a tendency to be low, and there was only a slight increase following the test meal. The cholesterol ester-free cholesterol ratio was low in the first sample and decreased during the tolerance test period.

CASE 5.—In this case, the samples of blood taken during fasting and at eight hours revealed a definitely low percentage in the neutral fat fraction, with a moderate increase in the percentage of total cholesterol. The cholesterol ester-free cholesterol ratio was decreased. There was a decrease in total cholesterol following the test meal.

CASE 6.—This case presented hyperlipemia with a moderately low percentage of phosphatides and a slight increase in the total cholesterol ratio.

CASE 7.—In this case the relative values of phosphatides and cholesterol were moderately increased; the neutral fat, soap and fatty acid fraction was significantly decreased, and there was a marked disturbance in the cholesterol ester-free cholesterol ratio.

CASE 8.—The sample taken during fasting showed a high phosphatide and cholesterol content with a decidedly low neutral fat, soap and fatty acid fraction. There was only 36 per cent esterified cholesterol. In the tolerance test the total blood fats increased about twofold, with a normal distribution of the other constituents. However, the cholesterol ester-free cholesterol ratio always remained less than 47 per cent, and in the last sample the cholesterol esters comprised only 28 per cent of the total cholesterol.

We were able to obtain a large amount of xanthomatous tissue from case 1 and subjected it to the same type of analysis as the samples of the blood. A weighed sample of the fresh tissue was extracted for several hours with the

alcohol-ether solvent used for the serum. The results of the analysis expressed in milligrams per hundred grams of fresh tissue are given in the accompanying table. We found that 25 per cent of the total lipid content was cholesterol of which 87.8 per cent was cholesterol esters. Cholesterol was present to the extent of 3.6 per cent of the fresh tissue. The percentage of total lipids in the tissue was 14. Wile, Eckstein and Curtis found from 9 to 12 per cent total lipids of which 16 per cent was cholesterol.

COMMENT

In comparing the observed distribution of the lipid constituents in this investigation with accepted values for normal serum, one notes the rather wide variations in the concentrations of the various fractions that have been reported in the literature for normal serum. Peters and Van Slyke [12] gave the results of a number of investigators, showing the maximum and minimum values for the concentrations of the lipid fractions. From the table it can be seen that the neutral fat, soaps and fatty acid fraction comprises about 50 per cent of the total lipid content. This value, however, is subject to a normal 10 per cent variation in either direction. Likewise, the phosphatide content represents about 30 per cent and the total cholesterol about 20 per cent of the lipid content. Both of these values are subject also to a variation of at least 10 per cent in the former and 5 per cent in the latter case. Therefore, in interpreting the results obtained in this study, we consider them to be significant only when the neutral fat fraction does not fall within from 40 to 60 per cent of the total lipid content; the phosphatide content not within from 20 to 40 per cent, and the cholesterol not within from 15 to 25 per cent. Bloch's [2] normals are of about this magnitude, but he does not seem to allow for any normal variation.

On examination of the samples obtained during fasting from the patients studied, one notes that there is a variation from the normal in all cases. In six of the eight cases the neutral fat fraction was distinctly greater or less than the accepted 40 to 60 per cent distribution. In five of the cases there was a disturbance in the phosphatide fraction, and in five of the cases the cholesterol fraction was either high or low. In case 3 only, by these standards, would a normal distribution be interpreted. Aside from the gross disturbances in the relative proportions of the aforementioned constituents, Bloch [2] and his colleagues laid great stress on the effect of variations in the ratio of cholesterol esters to free cholesterol, which, according to Spranger,[7] markedly controls the stability of an oil-water emulsion, such as is present in serum. Spranger's results show that of the total cholesterol present, about 60 per cent must be esterified in order to maintain a stable oil-water emulsion (Peters and Van Slyke gave from 40 to 70 per cent). Any deviation from the normal cholesterol ester-free cholesterol ratio tends to render the oil-water emulsion unstable, leading eventually to an actual change of phase, i. e., to a water-oil emulsion. If we allow for a possbile maximum normal

variation in this ester fraction of from 50 to 70 per cent, and consider our cases from this angle, we note that case 3, which showed a normal gross distribution of lipid constituents, had an ester content of less than 50 per cent. Of the remaining seven cases, one showed an ester value greater than 70 per cent while five cases showed values less than 50 per cent for the cholesterol ester fraction. In all cases, then, there is a disturbance in either the gross relationship of the lipid constituents or in the cholesterol ester-free cholesterol ratio.

While we believe that the theory propounded by Schaaf and Werner as to the formation of xanthomas is sound, we cannot subscribe to the fact that serum analyses per se (no matter what methods of analysis are used) allow unquestionable deductions as to the stability or instability of the oil-water emulsion which must exist if these xanthomatous lesions are to form. To us it appears possible that there are many other constituents in the blood serum which might play a major part in the production of a stable or unstable oil-water emulsion, e. g., the serum proteins, calcium and sodium soaps of the fatty acids and other unknown emulsifying or deemulsifying agents. Therefore, it is our opinion that the only entirely satisfactory way in which to detect the possible presence of an instability in the oil-water emulsion in these serums, as it probably exists in these cases, is to show that the unstable emulsion may be more easily broken than are the emulsions that exist in normal serums.

With this idea in mind, several experiments were tried with serum from some of the eight cases, and the results obtained were compared with those from the serum of normal persons. In this connection, we used a number of commercial products designed to break oil-water emulsions that are encountered in the production of petroleum. Both the normal and the pathologic serums were treated with varying amounts of these emulsion breakers; they were then allowed to stand for several hours, and finally were centrifugated. In no instance was a breaking of the oil-water emulsion detected. A number of other well known methods for breaking oil-water emulsions were tried, with similar negative results. Even in cases in which the chemical analysis showed a great disturbance in the lipid fractions, no instability of the emulsion could be detected. It is our opinion, then, that even though analyses of the type used in this investigation would seem to show some instability in the emulsion of the blood fat in the water of the serum, actual physical disintegration of the emulsion cannot be shown by employing well known emulsion breakers. It seems plausible that with a disturbance in the lipid fractions a very slight instability might exist which might be intensified under the influence of some trauma or other alteration in the tissue, thus completing the disintegration of the emulsion and allowing the fats, phosphatides and cholesterol to deposit in the skin. The investigation of this phase is being continued by us.

It is not yet certain that the results of a cholesterol tolerance test are absolutely dependable. While the usual result of this test in persons without a disturbance of their fat metabolism is a temporary increase in the blood cholesterol, it is still open to question whether the failure of such an increase can be interpreted as pathologic. In this regard, we refer to Urbach, Epstein and Lorenz'[15] study of a unique case of extracellular cholesterosis in which both the normal control case and the patient failed to show a hypercholesteremia following a cholesterol-olive oil meal. As a consequence of this result, Urbach and his collaborators stated that the greatest caution should be exercised in the interpretation of a cholesterol tolerance test.

We call attention to this moot point in the results of the cholesterol tolerance test since in cases 1 and 5 of our series there was no increase in the total cholesterol value following the test meal. Both cases, however, showed other significant abnormalities in the lipid partition.

CONCLUSIONS

1. Three cases of xanthoma multiplex and five cases of xanthelasma examined by us showed disturbance of the fat metabolism.

2. This disturbance is indicated by an abnormal distribution of the lipid constituents of the blood or by the results of fat tolerance tests.

3. The findings of Schaaf and Werner in similar cases are corroborated.

4. The theory of Schaaf and Werner that the abnormal distribution of the lipid components of the blood indicates a relative instability of the blood emulsion which favors the formation of xanthomatous deposits appears to be the most plausible explanation of the pathogenesis of the formation of xanthomas yet propounded.

This hypothesis, however, has certain weaknesses which are discussed. Until these weaknesses are satisfactorily explained, unqualified acceptance of the hypothesis cannot be given.

ADDENDUM

Through Dr. Sidney J. Wilson of Fort Worth, Texas, we have been able to examine the blood of a patient of his with xanthoma multiplex. This was done after the completion of our paper.

The patient was a woman, 20 years old. Her height was 5 feet and 8 inches (172.7 cm.); her weight, 118 pounds (53.5 Kg.). Her health had always been good. The duration of the eruption was four months. It began on the abdomen and had gradually become generalized. The lesions began as small, brown papules which gradually increased in size. As they enlarged they became chamois-colored. Biopsy was not made.

15. Urbach, E.; Epstein, E., and Lorenz, K.: Arch. f. Dermat. u. Syph. **166**: 243, 1932.

A general physical examination showed no abnormalities. Urinalysis gave negative results. The blood sugar was 105.6 mg. The sample of blood taken after a suitable diet and fast showed: total fats, 710 mg.; neutral fats, 13.8 per cent; phosphatides, 66.2 per cent; cholesterol, 20 per cent, and cholesterol ester, 61 per cent. This revealed a derangement of the phosphatide fraction, which was greatly increased. The neutral fats were definitely low. The absolute and relative quantity of cholesterol was normal, as was also the cholesterol ester-free cholesterol ratio.

ABSTRACT OF DISCUSSION

DR. FRED D. WEIDMAN, Philadelphia: I am in sympathy with the conclusions drawn by Dr. Michael. Many of us were made aware of this hypothesis by the presentation of a large collection of reprints representing some of the work done in Bloch's clinic. By this time it has been amply demonstrated that there is such a thing as an imbalance of blood lipids, and Dr. Michael has again demonstrated it preliminary to his more advanced studies. It occurs in diabetes in which there are notorious disturbances of fat metabolism, and in leukemia in which disintegration of leukocytes is prominent. Bloor leans to the idea that even "mutation" of fats can occur; i. e., neutral fat may change into one of the soaps. That is, the presence of cholesterol in the blood is the result not only of cholesterol ingested in the diet, but also of metabolic and other changes.

That, however, takes us only part way. After that, it remains to determine more accurately whether certain stable or unstable combinations of emulsions of blood fat can be produced. We know that a simple upset of blood lipids owing to the ingestion of cholesterol (cholesterol cramming of rabbits) does not necessarily lead to the development of xanthoma. One effect of Dr. Michael's contribution will be to set our feet more firmly on the ground and keep us from being swept away regarding the rôle of instability of fat emulsions as the controlling factor in causing xanthoma and to make us aware that the subject of xanthoma is not closed. Many more items regarding the metabolism of fats will be necessary before we come anywhere near an understanding of the pathogenesis of xanthoma.

DR. WALTER J. HIGHMAN, New York: I wish to recall to Dr. Michael that about twenty years ago Lebedev published a paper on experimental xanthoma. He fed lipids, I think lecithin, on lettuce leaves to rabbits. He placed setons in the the skin of his experimental animals, at which sites alone the xanthomas appeared. Of course, human beings in whom xanthomas develop do not have setons placed in the skin, but it is obvious that a local as well as a general factor is involved in the process. Is there anything new in the literature, with which Dr. Michael is no doubt familiar, that can throw further light on this phase of the question?

DR. JEFFREY C. MICHAEL, Houston, Texas: I agree with everything Dr. Weidman said about this subject. The explanation of the formation of xanthomas is as follows: Primarily a disturbance in the liver, or perhaps in the central nervous system, which leads to a disturbance of the lipid metabolism takes place. The latter is shown by suitable methods to be an imbalance of the blood lipid constituents, producing an unstable fat emulsion. This unstable emulsion is deemulsified under certain changes in the tissues with the deposition of lipids. The story is not as simple as that, for Dr. Nicholas has found a lipid imbalance in one case of nephrosis and in one of acute yellow atrophy of the liver. In neither case were there xanthomatous deposits. From these experiences it appears that further work is required to settle the validity of the hypothesis of Schaaf and Werner. As to Dr. Highman's question, I cannot answer it categorically, but I believe that cholesterol may act as a foreign body.

"CONSECUTIVE" DEPIGMENTATION

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Several dermatoses at times are followed by depigmented spots on the sites of the former lesions. These most often occur following syphilis and psoriasis, but also occasionally are seen after tinea versicolor, neurodermatitis and lichen planus. They may occur after any dermatosis of sufficient duration and depth to affect the pigment-forming cells in the basal layer of the epidermis. According to Feldman,[1] "every skin disease which is accompanied by scale or crust formation may give rise to leukoderma solare." He reported a series of cases in which patches of leukoderma developed following sun baths. The patients had pyodermia, seborrheic dermatitis and trichophytosis. Different diseases were followed by different types of leukoderma. He felt that leukoderma of this type, which he called leukoderma solare, was due merely to the screening effect of the overlying scale or crust. Achromic spots may also occur on the sites of previous lesions on covered parts of the body which have not been exposed to the sun. The diagnosis of this type of depigmentation is often difficult. It is first necessary to differentiate this secondary depigmentation from primary leukoderma, or true vitiligo. The following points are of importance:

"Consecutive" Depigmentation	Leukoderma
1. History of antecedent eruption on same sites as depigmented spots, or remains of lesions elsewhere on the body.	1. No antecedent eruption. Depigmented spots appear spontaneously on previously normal skin.
2. Patches same size and shape as previous lesions.	2. No previous lesions. Patches of various sizes and shapes.
3. Usually no hyperpigmentation of edges (except in syphilis and at times following tinea versicolor).	3. Hyperpigmentation of edges almost always present, except in an involuting patch.
4. No associated metabolic or endocrine disturbances or alopecia areata.	4. Metabolic and endocrine disturbances and alopecia areata often present.
5. Patches not symmetrical unless preceding lesions were.	5. Patches usually symmetrical.

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1. Feldman, A. A.: Ueber das Leukoderma solare, Dermat. Wchnschr. **80**: 117 (Jan. 24) 1925.

6. Most often on covered parts of the body.	6. Most often on exposed parts (face and dorsa of hands and wrists).
7. No hereditary factor.	7. Heredity apparently a factor in some cases.

Secondary depigmentation must also be distinguished from scleroderma, morphea, lichen albus atrophicus and "white spot disease." The differential points are:

"Consecutive" Depigmentation	Scleroderma, etc.
1. Patches flat.	1. Patches are usually slightly elevated.
2. No atrophy	2. Atrophy usually present.
3. No infiltration. Consistency of skin is normal.	3. Skin over patches is usually thickened.
4. Border sharply outlined and color of normal surrounding skin.	4. Border usually indistinct and shades off gradually into normal skin. In morphea, there is usually a delicate pink or violet ring around the patch.
5. No telangiectasia.	5. Telangiectasia characteristic of scleroderma and morphea.
6. Spots at sites of previous lesions.	6. No previous lesions.
7. Histology normal except for lack of pigment.	7. Characteristic histologic picture of hypertrophic connective tissue followed by atrophy of blood vessels and epidermis.

The maculo-anesthetic type of leprosy can be distinguished by the presence of anesthesia in the achromic spots, the history of possible exposure and, at times, by a positive nasal smear, the presence of other manifestations of the disease and the characteristic pathologic process. In extensive cases of chloasma and other pigmentations, it is necessary to determine the color of the normal skin and to realize that one is dealing with pigmentation rather than depigmentation. In persons with very light skin, the normal skin may appear depigmented in comparison with surrounding areas of pigmentation.

Partial albinism can be easily distinguished from consecutive depigmentation by the characteristic appearance of the former, the lack of pigmentation of the hair and iris, the family history and the presence of the condition since birth.

Probably the best known and most common example of consecutive depigmentation is that which is associated with syphilis and is known as leukoderma syphiliticum. This usually appears on the sites of former syphilitic lesions but may appear on previously normal skin, as is seen in the classic cases of leukoderma coli. The latter condition is con-

sidered by many authorities to be pathognomonic of syphilis. As the name implies, this occurs on the neck. It consists of many tiny, round or oval, ill-defined, depigmented spots with hyperpigmented borders and gives a markedly mottled appearance to the skin. It is seen most often in girls and brunettes. These spots may persist for many months after the rest of the eruption has disappeared under treatment. Occasionally, this is the only evidence of the disease on the skin. Late secondary and tertiary lesions and gummas, on healing, often leave depigmented spots with hyperpigmented borders. The presence of such patches with the history of previous lesions on the same sites should always make one suspicious of syphilis.

Patches of psoriasis are also occasionally followed by depigmentation. This occurs most frequently after treatment with ultraviolet radiation, sun baths or chrysarobin. These white spots are striking compared with the surrounding normal skin which is tanned or stained with chrysarobin. Some think that the lack of pigmentation in these spots is due merely to mechanical protection by the scales against the tanning of the sun or the staining of chrysarobin; others consider that in psoriasis as in syphilis, in some cases, there is a toxic disturbance of pigment formation, starting as an overstimulation and finally resulting in an exhaustion of pigment-forming powers. In favor of the first theory is the fact that in many instances the pigmentation in these patches can be restored to normal by erythema doses of ultraviolet light, or the mottled appearance disappears as the tanning or staining of the surrounding normal skin fades out. Beron [2] presented a boy, aged 10, with patches of psoriasis of six months' duration. These appeared in the fall, following frequent sun baths during the previous summer. At the time of examination he had white spots, symmetrically located on each lumbar region, and typical, scaly, red spots on the front of the thighs. Later, white spots appeared on the chest and buttocks. There were a few patches of psoriasis on the arms and legs. Only a few of those on the legs were followed by vitiligo. Beron gave this patient no treatment and was able to watch the stages of development from psoriasis through leukoderma psoriaticum to true vitiligo. He did not think this was merely a coincidence of the two conditions, but felt that the sun baths were responsible for the psoriasis and subsequent vitiligo.

The various forms of eczema, especially the chronic, lichenified, circumscribed type, may be followed by depigmentation. Cleveland [3] reported a case of leukoderma associated with lichenification, occurring

2. Beron, B.: Clinical Aspect of Postpsoriatic Depigmentations, Dermat. Wchnschr. **91**:1161 (Aug. 9) 1930.

3. Cleveland, D. E. H.: Leukoderma: Report of Unusual Case Associated with Lichenification, Arch. Dermat. & Syph. **18**:527 (Oct.) 1928.

in a girl aged 18. There were patches of leukoderma alone and lichenification alone as well as areas in which both conditions were present. The most interesting and unexpected finding in this case was that after a few fractional roentgen treatments of the itchy lichenified areas the pigment began to fill in along the edges. This was surprising since depigmented, as well as hyperpigmented, areas often occur on the sites of patches of chronic lichenified eczema which have disappeared after roentgen therapy. Werther [4] reported the case of a 39 year old lithographer with eczema of the hands and forearms. Six months later, a large white area with no hairs or pores in the center and with a hyperpigmented border appeared symmetrically along the ulnar side of each forearm. The border was hypersensitive and lichenified and the white center was hyposensitive. The author believed that the occurrence of vitiligo is associated with changes in sensitivity of the superficial nerves. The white areas in this case did not occur exactly on the sites of the former eczema and did not appear on the sites of suppurating scars. Jordan [5] and Moscow reported a case of vitiligo associated with a dermatitis due to mercury. In both these cases, the vitiligo may have been coincidental and not secondary to the dermatitis.

On account of the chronic and often violent and deep scratching, with consequent disturbance of the pigment-forming layer, pruritus vulvae and ani quite often are associated with depigmented patches. Although hyperpigmentation is the common finding, patches of dermatitis herpetiformis and lichen planus at times may be followed by depigmented spots.

Small irregular areas of depigmentation, as well as hyperpigmented spots, are seen in areas of radiodermatitis. Both of these probably are due to disturbance and destruction of the pigment-forming cells. Cannon [6] presented a man, aged 47, with pigmented and white spots, varying in size from that of a pea to that of a palm, at the sites of former lesions of erythema multiforme bullosum. The patient had taken no arsenic.

The form of achromia about which most of the recent literature on this subject has been written is called achromia parasitaria or pseudoachromia postparasitaria, according to the author's conception of the etiology. In 1923, Pardo-Castello and Dominguez [7] used the former title, which was Jeanselme's original name, in describing their obser-

4. Werther: Ueber nach Chromsäuredermatitis entstandene Vitiligo mit überempfindlicher lichenoider Randzone, Dermat. Wchnschr. **90**:766 (June 7) 1930.

5. Jordan, quoted by Werther.[4]

6. Cannon, A. B.: Erythema Multiforme Bullosum with Pigmentation and Vitiligo, Arch. Dermat. & Syph. **24**:673 (Oct.) 1931.

7. Pardo-Castello, V., and Dominguez, M.: Achromia Parasitaria, Arch. Dermat. & Syph. **9**:82 (Jan.) 1924.

vations on thirty-six cases of an eruption starting with dirty white, somewhat itchy, slightly inflammatory spots. The inflammation soon disappears and the spots become scaly, but later completely lose their scales. In the last stage, they appear as white spots covered by apparently normal epidermis and resembling leukoderma syphiliticum. Some familial cases seem to indicate a contagious factor. The authors obtained an aspergillus in pure culture in the lesions from six patients, although several attempts at auto-inoculation gave negative results. The disease is very resistant to treatment, but in some cases is cured with strong parasiticidal remedies.

In 1932, Pardo-Castello[8] summarized the three theories as to the etiology of the disease: (1) it is the result of the action of the short rays of the sun, tanning normal skin and leaving apparently depigmented spots in places which happen to be protected by a patch of tinea versicolor; (2) the disease is a true depigmentation caused by the destruction of parasites by the short rays of the sun; (3) the depigmentation is the result of the presence of the fungus itself. He reported that since his first paper the same aspergillus as well as other, different fungi had been found. For this reason, he considers that achromia parasitaria represents a group of epidermomycosis due to different fungi with more or less similar clinical pictures but varying according to the patient, race and country. He stated that "this group of dermatomycosis comprehends those cases reported as achromie parasitaire à recrudescence estivale, tinea flava, tinea alba, achromia parasitaria and perhaps many cases indistinguishable from pityriasis versicolor," and he gave credit to Jeanselme for first describing this condition under the first title. Pardo-Castello thinks that short wave rays play little or no part in the achromia and that this is most likely due to a biologic, or perhaps mechanical, action of the fungi themselves on the pigmentary mechanism of the skin. In confirmation of this theory is the fact that the condition is often found in Negroes with very black skins, which are not affected by the sun, and also on covered parts of the body. The long duration of the achromia also points to a permanent disturbance of pigmentation. The frequent cure of these achromic patches by strong antiparasitic remedies suggests that they are caused by the fungi and not by mechanical filtration of the sun's rays. Histologically, there is absence or decrease of pigment in the basal layer of the epidermis, with scattered lumps of pigment in the papillary layer and deep in the cutis. The disturbance of pigmentation in this condition is similar to that causing the discolored patches often following the epidermic inflammation in eczema, dermatitis seborrhoeica and impetigo.

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8. Pardo-Castello, V.: Achromia Parasitaria: Its True Nature and Etiology, Arch. Dermat. & Syph. **25**:785 (May) 1932.

Pardo-Castello concludes that achromia parasitaria is a secondary phenomenon in the evolution of a group of epidermomycoses in which the causative fungi disturb the normal process of pigmentation of the skin.

Castellani [9] considered that achromia parasitaria was synonymous with tinea flava and that in certain cases the fungus had a deep, almost permanent, disturbing action on the pigment of the skin, even after it had been destroyed.

Barney [10] presented a white girl, aged 16, who six months before first noticed brown, scaly, itchy patches over her trunk. Three months later, she took sun baths, and the brown spots disappeared, leaving white areas. One month after this, examination of her chest and back revealed several large depigmented areas with convoluting borders suggesting the confluence of smaller areas. There were similar satellite lesions, varying in size from that of a pinhead to that of a quarter, but no scaling or infiltration. Repeated examinations of skin scrapings showed no fungi, but one month later, typical tinea versicolor appeared on the trunk, and scrapings were positive for Microsporon furfur. At the same time, numerous small pea-sized, white macules appeared on her arms and new lesions on the old white areas. The latter did not become pigmented in spite of treatment. Howard Fox [11] also presented a patient with pityriasis versicolor followed by apparent depigmentation. The fungi were found in both the tan and white spots. On account of the development of achromic patches in spite of protecting a part of the skin from short wave rays with an opaque disk, Artom [12] felt that he had proved that the achromia was a true depigmentation. He thought that the fungi had an antiphotosensitizing action, or that perhaps depigmentation was due to inflammatory phenomena. Gougerot, Joyeux and Arnaudet [13] felt that these achromias can be explained by the reversal of the photocatalytic reaction of the mycoporphyrins present in the fungi in the scales. They reported a case of achromia parasitaria in a North African Arab. The first two authors and others thought that the ultraviolet rays discolored the colored patches of tinea versicolor and that the achromia was a true one and not due merely to contrast

9. Castellani, A.: Fungi and Fungous Diseases, Arch. Dermat. & Syph. **17**:215 (Feb.) 1928.

10. Barney, R. E.: Pseudo-Achromia Postparasitaria—Tinea Versicolor, Arch. Dermat. & Syph. **25**:1167, 1932.

11. Fox, H.: Pityriasis Rosea Followed by Apparent Depigmentation, Arch. Dermat. & Syph. **15**:751 (June) 1927.

12. Artom, M.: Contributo allo studio della pityriasis, versicolor acromizzante, Gior. ital. di dermat. e sif. **71**:1945 (Dec.) 1930.

13. Gougerot; Joyeux and Arnaudet: Un cas d'achromie parasitaire nord africain, Bull. Soc. franç. de dermat. et syph. **37**:110 (Jan.) 1930. Gougerot; Joyeux and others: Achromies "parasitaires" ou mieux épidermomycoses achromiantes, ibid. **36**:1028 (Nov.) 1929.

between the normal and surrounding pigmented skin. They stated that achromia parasitaria had become frequent in France, and they proved by experiment that it was an atypical form of tinea versicolor. Malassezia furfur was found in the patches. Mantarro [14] isolated Hemispora stellata in six cases of an achromic condition. He was in doubt as to the mode of action of the fungus.

Kistiakowsky [15] is an exponent of the physical cause of this condition. He concludes that the achromia is postparasitic and due to the contrast between the sunburned normal skin and the normal skin protected by the growth of fungi. He stated that the parasite dies through the action of the ultraviolet rays, and the scaling ceases because of the disappearance of the parasite which causes it. The scales filter the rays, protect the skin and produce the white spots. He considers the mechanism physical and not biologic. According to Sutton,[16] Florey, Wertheim, Almkvist and others also feel that the white patches are due to protection of the normal skin from the sun by the scales of tinea versicolor and other parasitic diseases of the skin. In pinta, a parasitic dermatosis endemic in the tropics, the patches after four or five years become white and atrophic and may simulate achromia parasitaria except for the absence of atrophy in the latter.

Michelson [17] reported the case of a girl, aged 17, who at the age of 11 noticed that her eyebrows and lashes were becoming white and that circumscribed, brown-pigmented spots with very white intervening skin began to develop over her body. This condition had not changed for a year. No other members of the family were similarly affected. Bloch considered this condition due to hypo-active pigmentary function in one area and hyperactive function in another. The occasional occurrence of a patch of vitiligo with a pigmented nevus in the center is another manifestation of disturbance of the distribution of pigment. In these cases, it might be assumed that the great excess of pigment in the central nevus caused an exhaustion of pigment in the surrounding areas with the resultant vitiligo.

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14. Mantarro, G.: Epidermomicosis acromizzante da hemispora stellata, Gior. ital. di dermat. e sif. **72**:131 (Feb.) 1931.

15. Kistiakowsky, E. W.: Pityriasis Versicolor and Ultraviolet Rays: Achromia Cutis Postparasitaria, Arch. Dermat. & Syph. **15**:695 (June) 1927; L'achromie, qui apparait sous l'action des rayons ultra-violets du soleil sur le pityriasis versicolor, este-elle parasitaire ou post-parasitaire? Ann. de dermat. et syph. **1**:1264 (Dec.) 1930.

16. Sutton, R. L.: Disease of the Skin, St. Louis, C. V. Mosby Company, 1926, p. 589.

17. Michelson, A. G.: Ephelides with Associated Vitiligo and Canities, Arch. Dermat. & Syph. **23**:394 (Feb.) 1931.

In a recent paper, Ludy, De Valin and Hart-Drant [18] reported depigmentation on the sites of lesions of pemphigus healed by viosterol. The similarity of the action of viosterol to that of sunlight, as well as the character of the lesions themselves, may explain the occurrence of achromia in these cases.

I need only mention the depigmentation in scars and burns, which is due to destruction of the pigment-forming cells as well as the other constituents of the skin.

REPORT OF CASES

The following case reports are given as examples of some of the more common forms of "consecutive" depigmentation:

CASE 1.—*Achromic Spots Following Furfuraceous Impetigo.*—R. B., a boy, aged 7, was seen on Feb. 24, 1933. The eruption started about eighteen months before, during the summer while he was at the seashore, with several scaly, depigmented patches on the face. These appeared and disappeared from time to time. They had not been treated except for the occasional use, for a short time, of 5 and 10 per cent ammoniated mercury ointment which had no effect. The patches were not itchy and had never been vesicular, crusted, purulent or oozing. The patient's mother had had two or three similar patches on her forearms, which had disappeared with a few applications of tincture of iodine. At the time of examination, there were four or five roughly round and circumscribed, slightly elevated, red, dry, scaly, lentil-sized patches on the lower part of each cheek. There was a very ill-defined, larger, slightly depigmented and scaly patch on the upper part of each cheek and on the nose. None of the patches were vesicular, crusted or oozing. Scrapings taken from several of the patches showed no fungi. The conscientious application of 10 per cent ammoniated mercury ointment for several weeks caused distinct improvement in the active spots, but little, if any, pigment returned in the depigmented patches. This case is interpreted as an example of more or less permanent depigmentation following patches of furfuraceous impetigo which were exposed to the sun. Although the patient's mother did not recall the presence of any previous lesions, it is assumed that they were present, since inflammatory patches as well as the white spots were seen at the time of examination eighteen months after the onset of the eruption.

CASE 2.—*Achromia Parasitaria.*—L. S., a white girl, aged 19, was seen in the dermatologic clinic of the New York Post-Graduate Medical School and Hospital on Nov. 19, 1932. At this time, she presented several small, round, white spots on the right side of the upper part of her back. They were not scaly or inflamed, and they had appeared two months before, after a sunburn. There were no previous lesions, and no other members of the family were affected. Microscopic examination of scrapings from the white spots was negative for tinea. She was given a 10 per cent solution of sodium hyposulphite, and the right side of the upper part of the back was exposed to an erythema dose of ultraviolet radiation. The patient did not return for observation. Although microscopic examination and culture of scrapings from the white spots revealed no fungi, on account of the absence of previous lesions and because the clinical picture so closely resembled that described by Pardo-Castello, a diagnosis of achromia parasitaria was made.

18. Ludy, De Valin and Hart-Drant: Viosterol in Treatment of Pemphigus, special reprint in cooperation with Mead Johnson and Company.

CASE 3.—*Leukoderma Syphiliticum.*—G. W., a mulatto woman, aged 30, married, born in the British West Indies, was first seen in the dermatologic clinic of the New York Hospital on Oct. 6, 1932. Scattered over her chest, back and abdomen, were numerous roughly round, nonscaly, depigmented spots, about 1 cm. in diameter, scrapings from which showed no fungi on microscopic examination. These spots appeared six years before, during pregnancy, at which time the Wassermann reaction of her blood was found to be positive. She then received a few intravenous and intramuscular injections during a period of two or three months. In spite of no further treatment, the spots decreased in size and number. From Oct. 6, 1932, to Jan. 13, 1933, she was given seven injections of arsphenamine. Although all the doses were very small, after each of the last four injections she suffered from one or more of the following: headache, nausea, vomiting, chills, fever or erythema. She then received twelve injections, of 2 cc. each, of bismuth salicylate. Following these, one small dose of arsphenamine and one of neoarsphenamine were given. Each of these caused a severe reaction. Since then, she has received five injections of sodium thiosulphate. On March 13, 1933, the Wassermann test of her blood was negative in both antigens, the Kline diagnostic test one plus and the Kline exclusion test three plus. Examination on June 23 revealed that the depigmented spots were as numerous as on admission, but there were apparently no new ones, and the contrast between these and the normal skin was less marked.

CASE 4.—*Achromic Spots of Unknown Cause.*—L. B. was first seen in the dermatologic clinic of the New York Hospital on Dec. 19, 1932. He complained of a small, slightly itchy lesion on the prepuce, which had been present for four days and which followed intercourse. Examination revealed a red, edematous, nonindurated, nonulcerated patch, 1 cm. in diameter, on the left side of the prepuce. There was no enlargement of the inguinal glands. The results of several dark-field examinations were negative, and the Wassermann reaction of the blood in both antigens and the Kline diagnostic and exclusion tests were all completely negative on three occasions. The patch disappeared in a few days, and a diagnosis of dermatitis was made.

This patient had a generalized condition on his trunk, arms and legs, consisting of many small, white, macular areas, varying from one-eighth inch to the size of a dime in diameter. These were not atrophic, thickened, scaly or inflamed; they gave no subjective symptoms, and had been present as long as the patient could remember. There had been no increase in the size of any of the spots nor any increase in their number. The patient could remember no antecedent eruption, and no one else in his family had a similar condition. There was brown pigmentation of the skin in both groins, on the inner sides of the thighs and on the flanks, which was not entirely due to contrast between the white macular areas and the normal skin. As these white spots were asymptomatic, after healing of the penile lesion the patient did not return to the clinic for further observation.

CASE 5.—*Tinea Versicolor.*—F. B., a white girl, aged 20, was first seen in the dermatologic clinic of the New York Post-Graduate Medical School and Hospital on Oct. 14, 1932. She presented several depigmented spots scattered over the chest, back, shoulders and sides of her neck. These were limited to sunburnt areas. The patient could not remember whether there had been any previous lesions on the sites of the depigmented spots, but at the time of examination no scaly, pigmented patches were seen. Microscopic examination of scrapings from the white spots revealed Microsporon furfur. The Wassermann test of the blood was negative. She was given a saturated solution of sodium hyposulphite, but did not return to the clinic for further observation.

CASE 6.—*Psoriasis with White Spots.*—S. R., a white woman, aged 27, was first seen in the dermatologic clinic of the New York Post-Graduate Medical School and Hospital on Nov. 5, 1932. She had scaly spots on her scalp and red, scaly, circinate spots over the sternum and upper part of her back. There were several small, white spots on the upper part of the back which had been present for eight months. She had had no treatment, and the white spots did not follow sunburn. She was given a 10 per cent ammoniated mercury ointment for the spots on the body and scalp. She did not return for further observation until December 24. At this time, the white spots were fainter; the scalp was very much improved, and the patches on the chest had entirely disappeared. The patient had used the ointment also on the white spots. On December 26 and January 21, ultraviolet rays from the cold quartz mrecury vapor lamp were applied for twenty seconds to the white spots on her back. The patient lived a long distance from the clinic and could not come for regular weekly treatments. On February 5, both the scaly red spots and the white patches on her back had almost disappeared. She has not been seen since.

CASE 7.—*Leukoderma Following Neurodermatitis Circumscripta.*—V. J., a Negress, aged 42, was first seen in the dermatologic clinic of the New York Post-Graduate Medical School and Hospital on Sept. 20, 1932. On the nape of her neck was a small, rather ill-defined patch of lichen chronicus simplex, consisting of several minute, shiny, itchy, lichenified papules. Slight depigmentation was seen in one spot. The patch disappeared after two roentgen treatments. About a month later, a dime-sized, roughly round, depigmented area appeared at the site of the previous eczema. The patient did not return to the clinic until Jan. 31, 1933. At this time, she presented a depigmented patch on the nape of her neck and a pea-sized, oval, depigmented patch extending symmetrically from each outer canthus. She first noticed the latter patches about two weeks before. There was no scaling or atrophy in the centers, and the edges were definitely hyperpigmented. A lentil-sized, depigmented spot appeared on the upper lip about one week before. The patient had had some miscarriages but no children. The Wassermann test of her blood was negative, and the sedimentation rate was 11 mm. per hour. She was given two injections of gold sodium thiosulphate for the vitiligo, but did not return for further treatment. This case is somewhat similar to Cleveland's in that neurodermatitis and leukoderma occurred in the same patient, although in this instance the depigmentation increased following roentgen therapy while in his patient the pigment returned.

CASE 8.—*Dermatitis Medicamentosa with White Spots.*—G. W., aged 42, was first seen in the dermatologic clinic of the New York Post-Graduate Medical School and Hospital on Nov. 2, 1932. He had epilepsy and had taken bromides for twenty years and phenobarbital for ten years. At the time of examination, he had many pustules, chiefly on the back, chest, buttocks and thighs, and several pea-sized, scaly, pigmented lesions over the rest of the body. There were several pustules and rosacea on the face and follicular pustules on the scalp. Scattered over the trunk and limbs were many small white spots. Microscopic examination of scrapings from both the scaly pigmented lesions and the white spots showed no fungi. The patient did not return after his first visit.

COMMENT

Apparently depigmented spots may be due merely to the contrast between the normal surrounding pigmented skin and the normal skin

protected from the sun's rays by the overlying scales or crusts of an antecedent eruption. True achromia may follow the local disturbing or destructive effect of any deep or chronic dermatosis on the pigment-forming cells. A third cause is a general toxic disturbance of pigment formation independent of the presence of previous lesions. The white spots following psoriasis, impetigo and tinea versicolor are usually examples of the first type. The proponents of the mechanical cause of achromia parasitaria place it also in this group, while others consider that the achromia in this disease is due to a local toxic effect on pigment formation. This would place it in the second group with the achromias following chronic lichenified eczema, lichen planus and similar conditions, although the mechanism in the latter diseases is probably more mechanical than toxic. Syphilis is the preeminent example of the third group, and the most typical form is leukoderma coli. Further study of these secondary depigmentations may throw some light on the still unknown cause of true leukoderma, although the latter is generally considered to be of neurogenic or endocrine origin and usually occurs on previously normal skin.

SUMMARY

1. The differential diagnosis is given between "consecutive" depigmentation and other dermatoses in which the depigmentation is primary.

2. The cases of different types of secondary depigmentation reported in the literature and the theories as to the cause of achromia parasitaria are reviewed.

3. Eight case reports illustrating different types of depigmentation are included.

4. Secondary depigmentation may be: (1) only apparent and merely due to contrast between untanned and tanned skin; (2) caused by a local mechanical, destructive or toxic effect, or (3) by a toxic effect on pigment formation in general.

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TUBERCULODERMAS OF THE FACE

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REVIEW OF THE LITERATURE

Tuberculous lesions of the face may assume any one of a large number of forms. To describe thoroughly and well all of these would be beyond the scope of this article; therefore, we shall discuss only the essential facts concerning the various lesions caused by the tubercle bacillus which may occur on the face.

The polymorphism of tuberculosis is surpassed only by that of syphilis, but in a study of cutaneous tuberculosis we have neither an accurate clinical course nor a test as reliable as the Wassermann test to depend on. In investigating lesions of suspected tuberculous etiology we have at our disposal the following methods: clinical history and examinations, morphology of the lesion, histology of biopsy specimens, tuberculin tests, blood cultures and inoculations of animals. One will realize that such an investigation is difficult and requires an evaluation of the facts discovered. To make a diagnosis of tuberculosis from a cutaneous lesion is not sufficient. The lesion must be classified, and here we are confronted with the lack of an international classification. We do not believe that a broad term such as tuberculosis cutis is sufficient for a final diagnosis. Because of the great variation in the severity, the course and the prognosis in cutaneous tuberculosis, we are firmly convinced that a more specific diagnosis is desirable.

Present day literature retains many of the older striking names which have been applied to various tuberculous conditions, and, no doubt, these should be used because they often designate the type of lesion and the localization, as for example the name "lupus pernio."

Whose classification should we accept? After a careful survey of the schemes used by the great authorities on this subject we believe that at the present time it is impossible to advocate any particular one, but it is highly advisable for clinicians and authors to be certain that they clearly understand the definitions and the synonyms for the lesions under discussion, for only then can there be a harmonious conclusion in these matters.

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Read before the Section on Dermatology and Syphilology at the Eighty-Fourth Annual Session of the American Medical Association, Milwaukee, June 16, 1933.

Let us examine some of the prominent classifications. In Professor Jadassohn's clinic,[1] cutaneous tuberculosis was classified under three headings:

1. Tuberculosis of the skin in the classic sense, which included lupus vulgaris, tuberculosis verrucosa cutis, colliquative tuberculosis and certain mixed forms.

2. Tuberculids, including lichen scrofulosorum, rosacea-like tuberculid, erythema induratum, papulonecrotic forms and lupus miliaris faciei.

3. Sarcoid reaction types embracing Boeck's and Darier-Roussy's sarcoids, lupus pernio and granuloma annulare.

Professor Kren[2] has much the same scheme. He uses three headings:

1. True tuberculosis of the skin. Under this he places lupus vulgaris, lupus pernio, colliquative tuberculosis, tuberculosis ulcerosa miliaris and miliary tuberculosis as transitional forms into the tuberculids.

2. Tuberculids. These include lichen scrofulosorum, papulonecrotic tuberculids, Boeck's lupoid, acne telangiectodes, subcutaneous sarcoid, erythema induratum and livedo racemosa (Adamson).

3. Diseases whose tuberculous etiology is not certain but probable. These are: granuloma annulare, lichen nitidus, angiokeratoma, various disseminated erythemas and lupus erythematosus.

Gans[3] uses the mode of dissemination of the bacilli to the diseased parts as a basis for his classification:

1. Forms which come forth mostly as progressive, single foci, including tuberculosis cutis luposa, verrucosa, colliquativa and ulcerosa.

2. Forms which extend by way of the blood stream, comprising tuberculosis cutis miliaris acuta generalisata, lichenoides, papulonecrotica, luposa miliaris disseminata, indurativa (typus Bazin, Darier-Roussy, Boeck), lupus pernio and angiolupoid.

Rost[4] in a learned and original way classifies cutaneous tuberculosis on a clinicomorphologic basis and on an immunologic basis. He uses three broad groupings: (1) tuberculosis ulcerosa; (2) tuberculosis luposa, colliquativa and verrucosa; (3) tuberculids.

It will be noted that although there is some variation, the seasoned clinicians are much in accord except in the case of the disputed forms. Lupus miliaris faciei is a good example of such a type, and the aforementioned authorities evidently do not view it in precisely the same way.

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1. Martenstein, H., and Noll, R.: Statistische Untersuchungen über die Tuberkulinreaktion, Arch. f. Dermat. u. Syph. **158**:409, 1929.

2. Kren, Otto: Die Tuberkulose der Haut, Wien. med. Wchnschr. **82**:1313 (Oct. 15) 1932.

3. Gans, Oskar: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, p. 419.

4. Rost, Georg A.: Hautkrankheiten, Berlin, Julius Springer, 1926, p. 84.

After all, these classifications are arbitrary and based on the morphology and clinical course of the lesions, the immunologic factor undoubtedly being kept in mind. To us the question of primary and secondary tuberculosis of the skin seems to be an important one. If the tubercle bacillus is the cause of all tuberculosis of the skin, the degree of tuberculous infection, or rather the power of resistance to the infection, must depend not so much on the clinical type evolved as on the factors that permitted or favored the development of that particular type. This leads one to ask pointedly whether or not tuberculosis of the skin is a primary infection, whether an internal focus is always present, and whether a tuberculous subject may not receive an external superinfection.

Our present knowledge does not permit us to make certain undisputed answers to these pertinent questions, for there are as yet no tenable laws which govern with certainty the development of tuberculodermas. The many cases of mixed forms reported are sufficient proof of this, but experience, minute observations, carefully made statistics, and deductions allow one a certain reasonable freedom in arriving at conclusions concerning these matters. The studies of allergy in cutaneous tuberculosis as carried out by that great master, Jadassohn, and by his disciples, the works of Ghon and Ranke in pulmonary tuberculosis and the writings of Kren, Volk, Dittrich, Rost and Bruusgaard point out many striking and well established facts. We learn that primary tuberculous infection of the skin is rare, that almost all cutaneous tuberculosis may be attributed to an internal focus, and that a tuberculous bacillemia is a reality even though an actual demonstration of the bacilli in the circulating blood is not always possible. Furthermore, the factors which mobilize the organisms and the reasons why, when circulating, the bacilli seek certain tissues in which to multiply are not known. We predict what the reaction of the tissue will be which will result in a particular type of demonstrable lesion. No doubt such varied factors as the number of bacilli, the vulnerability of the local tissues, the season of the year, the geographic location, the general resistance, race, sex and constitutional type of the host, the state of nutrition in the chemical sense and many other influences play a part.

The tissues of the face are more often the seat of tuberculodermas than any other part of the body. Almost every known type of cutaneous tuberculosis has been found on the face, but, to be sure, certain forms by far outnumber the others. We list the tuberculodermas of the face which we either have encountered ourselves or, in the very rare forms, have investigated in the literature. We have not attempted to evolve a classification as much as we have tried to enumerate the diverse entities which may arise from an identical etiologic factor.

THE TUBERCULODERMAS OF THE FACE

The following is our list of tuberculodermas of the face:

1. Lupus vulgaris
2. Lupus miliaris disseminatus faciei
3. Tuberculids
   - A. Papulonecrotic } superficial
   - B. Rosacea-like } deep
   - C. Lichen scrofulosorum
4. Sarcoids
   - A. Cutaneous
   - B. Subcutaneous
   - C. Angiolupoid
   - D. Lupus pernio
5. Tuberculosis colliquativa
6. Fungoid tuberculosis of Jadassohn-Riehl
7. Tuberculosis miliaris ulcerosa
8. Tuberculosis verrucosa cutis
9. Miliary disseminated lupus (exanthematous type)
10. Primary tuberculous complex of the skin
11. Rare or questionable forms
    - A. Granuloma annulare
    - B. Lichen nitidus
    - C. Livedo racemosa
    - D. Erythemas

The most striking thing that impresses one in undertaking a review of tuberculosis of the skin is the small number of cases of lupus vulgaris in America. In the European clinics the cases of lupus outnumber the sum total of all the other types of tuberculodermas many times over. In our clinics, on the other hand, the other types combined make a much larger aggregate than the cases of lupus. An explanation has not been found.

1. *Lupus Vulgaris.*—Lupus vulgaris is a true tuberculosis of the skin in that the bacilli can be found in a reasonably high percentage of searches, animal inoculations will usually yield positive results, and the histologic changes are accepted as being in keeping with those found in tuberculosis.

Lupus vulgaris is the most important example of cutaneous tuberculosis. It is a chronic form occurring in persons with a high degree of resistance; it is probably secondary to an internal focus even though this cannot be revealed, and it is characterized by the formation of the so-called lupus nodule, which is made up of a tuberculous infiltrate undergoing a fatty homogeneization accompanied by a certain amount of hyperemia. Under pressure with glass small translucent, reddish-yellow areas can be clearly seen; these are the so-called apple jelly nodules that are said to be pathognomonic for the condition.

Lupus vulgaris spreads by continuity; it is partially self-healing, but does not impart enough local immunity to the tissues involved to prevent recurrences within the scars formed. The severity of the process varies greatly as does the extent. The secondary pathologic changes and the anatomic location bring about certain modifications of type, producing such changed lesions as lupus vulgaris hypertrophicus, tumidus and verrucosus.

The face and neck are the most commonly involved areas. The extremities are next, while the rest of the body is only occasionally the seat of true lupus vulgaris. The nasal mucous membrane frequently shares involvement with the face, and the linings of the mouth as well as the tongue may be the seat of lupus.

As a rule, patients with lupus vulgaris react strangely to tuberculin. The Mantoux, Pirquet and Moro reactions are strongly positive locally

Fig. 1.—Classic lupus vulgaris.

even in large dilutions. Focal reactions are not so marked. Patients with lupus rarely succumb to internal tuberculosis.

The exact method by which the bacilli reach the skin, the manner of extension and the reasons for location on the face are not known. The recent statistics of A. von Mallinckrodt-Haupt [5] point to climatic and economic factors as being important. He found that far more cases in the Rhine provinces occurred in the poorer mountain districts, and they appeared more often in the cold months.

The differential diagnosis of lupus vulgaris from other forms of facial tuberculosis is quite simple. Characteristic are: the presence of lupus nodules, the contiguous lesions usually making up a plaque or large area of involvement which is distinctly localized; the chronicity with scarcely any tendency to spontaneous healing, and the lack of ulceration or formation of fistula, with practically no discharge.

2. *Lupus Miliaris Disseminatus Faciei.*—Lupus follicularis disseminatus faciei was the name which Tilbury Fox gave to a tuberculous

5. von Mallinckrodt-Haupt, A.: Die Hauttuberkulose in der Rheinprovinz, Dermat. Ztschr. **65**:295 (Feb.) 1933.

condition of the face observed by him in 1878. The name has been in common use since that time, and the condition, which is quite characteristic in its classic form, has been the subject of many articles. In later years Arndt [6] noted that all of the lesions were not follicular, so he eliminated "follicularis" from the title.

The lesions are discrete, small, yellowish-red, translucent papules which occur singly or in groups. The face is the common location,

Fig. 2.—Lupus miliaris disseminatus faciei.

especially about the eyelids, the cheeks and the mucocutaneous surface of the lips. There may be a certain amount of rosacea-like redness, and when, in such a case, the lesions have a central yellow point of softening, they look almost like either kind of acne pustules; however, by diascopy the true character is often, but not always, revealed. The surface is smooth. The lesions are soft, but do not sup-

6. Arndt, Georg: Ueber die Kombination von Lupus miliaris disseminatus faciei mit Acnitis und den Nachweis des Tuberkulose virus in Schnitt und im Antiforminsediment bei dieser Affektion, Dermat. Ztschr. **18**:53, 1911.

purate. The course is drawn out, and papules remain in about the same state of development for months, even though they may have appeared quite rapidly; no new lesions form by continuity from previous lesions. With a probe or a microcautery one can pass easily through the soft infiltrate and readily feel the hard surrounding tissue. Healing is spontaneous. The lesions gradually shrink away without a slough or a crust, leaving a small pitted scar. Tubercle bacilli have often been demonstrated in the sections.

The histologic changes are not constant, but depend to some extent on the time of the biopsy and the precise location of the section. In our own cases we have found a well demarcated globular infiltrate, made up of epithelioid cells, giant cells and lymphocytes, which was located high up in the corium. In some sections we found central necrosis, and in others a marked lymphocytic wall was seen about the inflammatory mass, blocking it off from the surrounding tissues. Kyrle stated that in histology lupus miliaris faciei more nearly resembled tuberculosis of other parts of the body than any other cutaneous type. This we have, of course, seen too, but only in the classic cases when the section passed through the center of a lesion.

Patients with this form of cutaneous tuberculosis usually react quite strongly to tuberculin; the Pirquet reaction was especially marked in one of our cases, while in another it was insignificant. In many reports of cases a state of positive anergy was described. The sensitivity to tuberculin might be an important differential finding in lupus miliaris disseminatus faciei.

The classification of lupus miliaris disseminatus faciei is not at all easy. The individual lesion is just like a small macule or papule of lupus vulgaris. The course is more chronic than that of acnitis. Certain small papular sarcoids are similar, but do not have the lupus-like appearance, and even though lupus miliaris faciei is chronic, sarcoid is even more so. This is a lesion of cutaneous tuberculosis which can be diagnosed and classified only by taking all the factors into consideration. The condition is closely related to lupus vulgaris and to sarcoid in the cases in which the course is slow; when the process is more rapid, the relationship is nearer to acnitis.

3. *Tuberculids.*—The tuberculids which occur on the face are classified according to the size and number of the lesions. The classic and most frequently mentioned type is so-called acnitis. Papulonecrotic tuberculids confined to the face are rare. More often the face is involved as part of a more or less general outbreak. The tuberculids typify the external projection of internal tuberculosis on a cutaneous screen. The bacilli are hematogenously disseminated and, because of unknown factors, lodge in certain areas and for a short time grow and flourish. The patients who have tuberculids have a high degree of allergy, as

evidenced by their behavior to the tuberculins. The lesions develop rapidly, are extremely labile and, accordingly, run a short course and disappear. If the location is quite deep and the necrosis marked, a scar remains to mark the spot. When the conditions are again ripe, a new dissemination of bacilli occurs, and a new crop of lesions is seen. The time between attacks may be long, even years, or one series of lesions may appear as the previous ones are healing. We have also seen a more or less continuous appearance and disappearance of sparse but widely disseminated papules.

Lewandowsky[7] described a rosacea-like tuberculid in which the lesions were very small, occurred in large numbers, and, because of a marked accompanying hyperemia, bore a striking resemblance to rosacea.

Fig. 3.—Rosacea-like tuberculid of Lewandowsky.

The lesions did not necrose or disappear on pressure with glass, and, microscopically, a tuberculoid process was present. There was a strongly positive local and general reaction to tuberculin.

Histologically the tuberculids, as a rule, are characterized by a central area of necrosis of the acute or rapid type, surrounded by a zone of inflammation which, especially at its periphery, may show tuberculous characteristics. The pathologic findings are quite uniform in type but not in extent.

To our minds the entire question of facial tuberculids is one of size, number, depth and precise location of the lesions and course. These points, with histologic and immunologic observations, are necessary to make a classification of any particular type.

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7. Lewandowsky, Felix: Ueber Rosacea-ähnliche Tuberkulide des Gesichtes, Cor.-Bl. f. schweiz. Aerzte **47**:1280, 1917.

There undoubtedly is a transition from one type of tuberculid to another. It is impossible for us to set down from a clinical and histologic point of view clearly defined criteria for the differentiation of superficial folliclis-like tuberculids from the larger and deeper acnitis.

The facial tuberculids are not in such close relationship to the other forms of cutaneous tuberculosis as is lupus miliaris faciei, for the tuberculids are quite distinct. On the legs, tuberculids are closely related to erythema induratum, but on the face they are quite unique in their isolation. They do not change much; this probably can be accounted for by their rapid course. The rosacea-like form is more chronic and

Fig. 4.—Miliary sarcoid. Note the lesions at the inner canthus of the eye and in the preauricular region. The scalp was also involved. The patient had tuberculosis of the spine.

does not necrose; we think that it is closely related to lupus miliaris disseminatus faciei, in fact much more so than to acnitis.

Disseminated papular sarcoid does not necrose; it is much more chronic and more indurated than the papules of acnitis.

When lesions occur on the face and are diagnosed as papulonecrotic tuberculids they should, and usually will, be found on other parts of the body such as the ears, the elbows, the dorsa of the hands and the toes. When they are present in these areas the diagnosis is more easily arrived at, but when the lesions are found only on the face, a most careful weighing of all the facts must be made before such a diagnosis is acceptable, and we believe that it will rarely be correct if the lesions are confined strictly to the face.

Lichen scrofulosorum rarely occurs on the face, and when it does, it is only as part of a generalized eruption. This condition should be grouped with the tuberculids and reacts in practically the same manner. The Moro test is valuable in this type of tuberculosis because of the local reaction. Lichen scrofulosorum, although frequently follicular, is not necessarily so. The microscopic picture contains all the elements that are necessary for a diagnosis of tuberculosis.

4. *Sarcoids.*—Lupoid or sarcoid is a form of indurative tuberculosis about which much has been written, and the variations of size, depth and form have allowed a classification based on these differences. The histologic changes of the established and fixed cases are quite constant and correspond to those of the epithelioid tuberculosis of the general pathologist. Often the lesions are composed entirely of closely packed epithelioid cells divided by septums of connective tissue; at times giant cells are present in varying numbers, and an encircling wall of lymphocytes is occasionally found. Necrosis and ulceration are never encountered. Certain sections of lupus vulgaris can be found which are identical with lupoid. Kyrle and Gans have demonstrated an early acute, unspecific phase in which tubercle bacilli have been found. The patient possesses a positive anergy, but arrested or partially checked foci of tuberculosis in the bones, lungs or lymph nodes are often discovered.

On the face, certain papular or nodular forms of lupoid have been seen in which a single lesion cannot be differentiated from lupus vulgaris or from lupus miliaris disseminatus faciei. Here again the diagnosis must rest on the decision made from the findings in the aggregate. One lesion and a section from a single location are not enough.

In a scheme of classification the lupoids are closely related to lupus vulgaris and to lupus miliaris disseminatus faciei. Their extreme chronicity, their indolence, their lack of subjective symptoms and the complete absence of ulceration coupled with a characteristic microscopic picture make the diagnosis relatively simple.

Here we must mention the fact that certain forms of cutaneous tuberculosis in the American Negro evidently are not entirely familiar to the continental observers. In the past few years colored patients with a generalized papular or discoid eruption, diagnosed as tuberculous, have been demonstrated before some of our dermatologic societies. Rauschkolb showed such patients before the Cleveland Dermatological Society. Tauber exhibited a Negress before the annual meeting of the Cincinnati Dermatological Society, and Senear and Nomland have shown a number of persons with such eruptions in Chicago. Recently Combes reported a case, and Stanley Crawford wrote on this type of condition in Negroes. The lesions were papular or small plaques which microscopically showed a sarcoid structure. The course was chronic without ulceration as in lupoid. In Crawford's case a severe tuberculosis with glandular

involvement developed, and microscopic sections of the glands showed a tuberculous type of pathologic process. The course of events here is somewhat different from the ordinary, in that the patients changed from anergic to allergic, which is quite the reverse of what is seen in the average case of lupoid. We believe that until these cases of more or less generalized, widely disseminated, papular forms of tuberculosis in Negroes are carefully studied and evaluated, it would be best not to arrive at a definite and arbitrary decision as to classification. Lupoid, at best, is a confusing clinical syndrome, and the variation of cases such as Schaumann has described as compared with the miliary lupoid that we have seen is so great that one would hesitate to include them all under precisely the same heading. The well known tendency to keloidal or connective tissue changes might account, in part, for the extreme firmness and indolence of these lesions in Negroes. At any rate, the cases shown appear to be a form of indurative epithelioid tuberculosis, and their subsequent history will be of great importance in making the final decision as to their position.

5. *Colliquative Tuberculosis or Scrofuloderma.*—Colliquative tuberculosis or scrofuloderma is a rather common form of tuberculosis of the face. This type of tuberculosis, as the name implies, is a form in which the lesions soften and discharge. It may arise primarily in the lymphatics of the skin, forming a cutaneous node which is gumma-like in appearance, or the skin may be secondarily involved from underlying lymphatic or osseous tuberculosis.

The diagnostic points concerning colliquative tuberculosis are well known. The blue color, the very thin adherent, overlying skin and the thin, watery pus oozing slowly or only on pressure from fistulous openings are quite characteristic. Bacilli can be found readily. The inoculation of animals often gives positive results, and the patient's sensitivity to tuberculin is about the same as in lupus vulgaris. There is more of a tendency to spontaneous healing than in lupus. This takes place more by means of a sloughing out or evacuation of the diseased area than by scarring as in lupus. Colliquative tuberculosis does not impart a high degree of local immunization to the surrounding tissues, for lupus vulgaris has often been found to develop about the ostia of the fistulas.

Other forms of cutaneous tuberculosis also develop in persons with the colliquative form; especially in our experience have we observed an associated erythema induratum. Many patients with a combination of colliquative tuberculosis and lichen scrofulosorum also have been reported.

In a classification tuberculosis colliquativa stands in close relationship to lupus vulgaris, to certain deep-seated, large-sized tuberculids

and to erythema induratum. A rare form of tuberculosis described by Jadassohn and Riehl, which is closely allied also to colliquative tuberculosis, is the following:

6. *Fungoid or Tumor-Like Form of Cutaneous Tuberculosis.*—This type of tuberculosis is extremely rare, and although it has been described by Riehl, Pick,[8] Nanta[9] and Jadassohn, their cases are not identical. Our own experience is limited to a single case which occurred on the hand and forearm of a woman 69 years of age:

> The lesions began as an extensive but fairly well defined red tumefied area which was slow to break down. The tumor-like swelling became elevated, consisting of several nodes as large as walnuts; the overlying skin was tense and blue, and finally an ulcer formed, covered with a black crust; on removal a deep ulcer with steep edges was revealed. The draining glands were enlarged. The lesion resembled an ulcerating sarcoma or an advanced lesion of mycosis fungoides. There was a slight tendency to heal. A bridge of epithelium and scar formed across part of the lesion. The microscopic section showed a tuberculoid structure; the sections stained for bacilli were negative. The Wassermann reaction was negative. Jadassohn stated that these patients react negatively to tuberculin, but that the prognosis is good. Our patient had a negative Pirquet reaction.

The type is unique clinically and may be classified in relation to colliquative tuberculosis purely on morphologic grounds.

7. *Tuberculosis Miliaris Ulcerosa.*—Tuberculosis miliaris ulcerosa is a severe form of ulcerating tuberculosis which occurs in persons with a severe form of systemic tuberculosis whose resistance is inadequate and whose sensitivity to tuberculin is either weak or entirely absent. The lesions occur exclusively about the nasal or oral orifices and are often associated with similar ulcers in the mucous membranes. Bacilli are easily found in direct smear; the histologic changes are distinctly tuberculous, and the lesions are not to be confused with other forms of cutaneous tuberculosis. They should be classified with the exanthematous form of miliary tuberculosis because of the lack of resistance of the host, and because of the ulceration and bacillary findings the lesions are in close relation to the primary complex. Certain severe forms of lupus vulgaris are also closely related to the ulcerating miliary form.

8. *Tuberculosis Verrucosa Cutis.*—The verrucous form of tuberculosis rarely occurs on the face, but the few cases that have been reported are important because of the question of primary infection and the so-called primary complex. Von Neumann[10] showed a case before

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8. Pick, Walter: Tumor-Like Forms of Tuberculosis of the Skin, J. Cutan. Dis. **22**:305, 1904.

9. Nanta, A.: Sur une forme du tuberculose fongueuse de la peau, Ann. de dermat. et syph. **5**:141, 1914-1915.

10. von Neumann, Isidor: Arch. f. Dermat. u. Syph. **63**:376, 1902.

the Vienna Dermatological Society in which the lesions occurred at the corner of the mouth. Riehl, Sr., in discussing this case emphasized the fact that the verrucous form of tuberculosis might begin as a phlegmon having a rather acute early course and then becoming more indolent and assuming the characteristic form of this type.

Histologically tuberculosis verrucosa cutis is characterized by the hyperkeratosis which always occurs, and by the underlying more or less typical tuberculous infiltrate in the upper portions of the corium.

Patients with tuberculosis verrucosa cutis as a rule react strongly to tuberculin, even in marked dilutions. In a scheme of classification this type is closely related to the verrucous form of lupus vulgaris and to the primary external forms of inoculation.

Fig. 5.—Tuberculosis miliaris ulcerosa in a patient with pulmonary tuberculosis.

9. *Miliary Disseminated Lupus (Exanthematous Type).*—This rare form of tuberculosis occurs in children most often following measles and is characterized by a widely disseminated papular eruption which readily and rapidly undergoes necrosis. The patients often succumb, and evidently their allergy is destroyed by the preceding acute infection. The face is not usually involved, and, if so, only with a few scattered lesions.

This form is related to the primary complex and to the ulcerating miliary form of tuberculosis and may be likened to acute miliary systemic tuberculosis.

10. *Primary Tuberculous Complex.*—Primary external infection of the skin with the tubercle bacillus, although rare, does occur. The classic description of this condition was made by Bruusgaard in 1926, but it was known long before that. Neumann reported before the

Vienna Dermatological Society, a good many years ago, seven cases of circumcision tuberculosis. Six of these infants died from the infection, and the seventh died later of generalized tuberculosis. Primary tuberculosis of the skin may be likened to Ghon's primary complex in the lung. At the port of entry a lesion is formed which is usually ulcerating, and the adjacent lymph glands soon become inflamed and may even suppurate. The bacilli may be demonstrated with ease from the secretion. The condition is at first much like an acute infection, and only from its persistence and chronicity does one begin to suspect that the etiologic factor is something aside from the ordinary pus formers. Many cases have been reported, and they all have approximately the same characteristics. Sometimes the ulceration becomes verrucous, and with this wartlike change the lesions look surprisingly like syphilitic

Fig. 6.—Possible primary tuberculous complex of the skin or tuberculous chancre. A single lesion with regional adenitis is seen (courtesy of Dr. O. S. Ormsby).

chancres. Stokes described, a number of years ago, what he called primary inoculation tuberculosis of the skin with metastases to the regional lymph nodes. There is a question whether his cases were primary inoculations of the skin, because of the age of the patients and the fact that systemic tuberculosis was not completely ruled out. Because of the tendency of primary tuberculosis to become verrucous, and because this type, as well as tuberculosis verrucosa cutis, has a decided tendency to spread by way of the lymphatics to the adjacent glands even causing a tuberculous lymphangitis, the two conditions may easily be confused, and, in fact, may be one and the same.

In order to use the term "primary" one must have fairly conclusive evidence that the subject has not had a previous infection. Therefore, the majority of authentic cases of primary cutaneous complex occur in young children, in whom sensitivity to tuberculin is not yet present; hence the destructive character of the lesion at first. Only after a

certain defense or allergy is acquired does the ulcerating lesion change to the less virulent verrucous type. Some of these patients have been followed, and the cutaneous lesion has proved to be the source of systemic tuberculosis.

The primary tuberculous complex in the skin is similar to that in other organs and is a very important clinical type because of the knowledge gained by observing the course of events in an initial implantation of tubercle bacilli in a nontuberculous host. Instead of a slowly developing indurative process, ulceration takes place early, caseation with softening soon results, and the perifocal lymph nodes become involved and may go through a similar process which results in suppuration. So it must be emphasized that the previous infection of the person with the accompanying allergy is probably the important factor in determining how the skin will react to new implantations. Primary infections are rare, and highly deceiving clinically. The histologic appearance, however, is that of tuberculosis.

11. *Rare or Questionable Forms.*—The etiology of granuloma annulare and lichen nitidus is not fixed definitely enough to be included in this article.

Certain tuberculous livedos and erythemas should be mentioned because the face is involved, but they are so rare that each case is worthy of a separate report.

COMMENT

In any topographic survey of tuberculosis of the skin one is immediately impressed with the great variation of the clinical picture. The classic types of tuberculosis, such as lupus vulgaris and colliquative tuberculosis, are easily recognized, and their course is well known. The more transient forms, especially when the lesions are small and run a fairly short course, are much more difficult to identify as belonging to a definite class. In the forms in which the lesions occur in crops, the diagnosis rests not only on the clinical findings but, unfortunately, on the microscopic picture of the lesion that is excised, and it must be emphasized that if multiple biopsies are made it is difficult to make a diagnosis. As Rost has aptly put it, tuberculosis of the skin may be compared to the spectrum, with all its variations in color. We have been impressed with the necessity of a procedure in diagnosing these conditions. We believe that it is best to try, first, to make a general diagnosis of tuberculosis cutis, and then after careful morphologic, immunologic and histologic studies, to attempt definitely to classify the lesion under one of the well known headings. The distribution, the main characteristics not of one lesion, but of all the lesions, a careful evaluation of susceptibility to tuberculin and an analytic viewing of the microscopic sections are necessary for arriving at a conclusion. We must

emphasize again the need for examining at least twenty-five sections, for we have been struck time and again with the great variation of sections which were taken from the same block. The clinical course, especially with regard to the spontaneous disappearance of lesions, and a careful observation as to scarring are of real value.

In histologic changes the various tuberculous lesions of the face, to be sure, have a striking similarity, and it would be utterly impossible to draw sharp lines based on histology which would separate definitely one type of tuberculosis of the skin from another. The differentiations are based on the preponderance of lymphocytes, epithelioid and giant cells and on necrosis. The depth of the infiltrate, the dimensions of the inflammatory zone and the secondary changes in the epidermis all influence one in arriving at a conclusion as to type.

There seems to be a definite connection between the site of predilection and the development of the disease, for example, in ulcerating tuberculosis of the mucous membrane or lupus pernio on the nose. The preponderance of any one of the trio of cells also has its significance. Dittrich [11] has commented on this, stating that the thickness of the lymphatic wall is an important indication of the direction of the inflammation, that the phases of tuberculosis are divided into an exudative and a productive phase, and that at the end of the exudative phase the productive phase takes the upper hand. He looks on the lymphocyte as the cell that is characteristic of the exudative advance, and on the epithelioid and giant cells as indicative of the productive period.

There is a definite relationship between the number of bacilli and the chronology. There is a proportion between the lymphocytic wall and immunity, for during the lymphocytic and exudative phase bacilli can frequently be found, while in the tuberculoid period the organisms are destroyed and cannot be demonstrated.

In lupus vulgaris one sees practically every phase of the reaction of the skin to an invasion by tubercle bacilli. The age of the lesion and the anatomic location, of course, influence the development. It is certain that the fresher a lesion is, the more lymphocytes are present, especially at the periphery of the infiltrate. The older the disease becomes, the more epithelioid and giant cells are to be found. The inflammation in lupus vulgaris begins, as a rule, in the papillary body, and it has been noticed that the higher the focus, the more readily are lymphocytes marshaled in defense. Early lupus vulgaris is sometimes difficult to diagnose, for it looks more like a chronic diffuse inflammation, but usually on examining serial sections, epithelioid cells will be found,

11. Dittrich, O.: Ueber den direkten Tuberkelbazillennachweis beim Lupus pernio und beim Sarkoid Boeck, Dermat. Ztschr. **60**:395 (April) 1931.

especially in the center, and in due course a tubercle will be formed. In cases which are clinically lupus vulgaris the microscopic picture can be identical with that found in lupoid of Boeck. Anatomic location also plays an important rôle, for where many hairs are present, giant cells develop more readily. Central necrosis or caseation is not a necessity for the diagnosis of tuberculosis. With elastic tissue stains most forms of tuberculosis of the skin will show the remnants of blood vessels in or near the center of the lesion. In fact, most cutaneous tuberculosis may be looked on as arising from a hematogenously borne infection.

Lupus miliaris disseminatus faciei occupies a position between lupus vulgaris and the tuberculids. In the typical microscopic example of this condition one sees the nearest approximation to tuberculosis as seen in other parts of the body that it is possible to find in cutaneous tuberculosis. The lesions occupy a position just below the epidermis and may, in fact, bring about a slight degree of atrophy but no other change. The lesions are oblong or spherical and are made up of the usual trio of cells; the lymphocytic surrounding wall is, as a rule, very thin or may be entirely absent. Epithelioid and giant cells are present in varying amounts. Serial sections of a mature lesion will nearly always show central caseation, and in this respect lupus miliaris disseminatus faciei is unique in tuberculosis of the skin. In fact, the necrosis is by far more constant in this type than in lupus vulgaris. Sections from the periphery of this form of lupus sometimes look surprisingly like lupoid of Boeck, and only after carefully reviewing the case clinically and surveying the serial sections can one make a definite differentiation. As a rule, in lupoid the lesion is sharply circumscribed and is deeply situated in the corium. Rarely is lupoid as consistently high up as lupus miliaris disseminatus faciei. Also, although lupoid may contain giant cells, they are not present so consistently or in such large numbers, and in lupoid of Boeck necrosis does not occur.

The papular necrotic tuberculid which occurs on the face, and which has been designated as acnitis and also as acne telangiectodes is a form of tuberculosis in which, typically, the tissue reacts strongly and forcefully against the infector. The microscopic observations are quite different from those made in the classic forms of tuberculosis. However, throughout the subject of tuberculosis of the skin one is impressed by the fact that the tubercle bacilli can and do call forth forms of inflammation which, though differing greatly clinically, are quite similar microscopically.

In reviewing the forms of tuberculosis which may occur on the face we believe that the variations in the clinical findings and the similarities in the histologic picture are impressive and show that the individual factors, each exerting its particular influence on the others, finally come

into a state of balance which allows the host to react in a certain manner against the invaders, and that the resulting lesions may pass through transitional phases before the predominating type comes into the majority. Then, and only then, can a final classification of type of cutaneous tuberculosis be made. In many cases this occurs rapidly, so that a diagnosis of a particular type of cutaneous tuberculosis is apparent from the beginning, but in a few patients a careful evaluation of all the pertinent observations is necessary.

ABSTRACT OF DISCUSSION

DR. MARION B. SULZBERGER, New York: It would be impertinent for me to try to add anything to the clinical exposition the essayists have given. They have observed closely, made an exact study and been fortunate in seeing many cases of tuberculosis. I should be at a loss to add one iota to their presentation in a clinical way. I think Dr. Michelson asked me to discuss this paper in the hope that I would say something about the immunology of the disease. But here I feel incompetent to give a clear summary in such a short time, for there is nothing more complex than the immunology of tuberculosis and tuberculids. There is probably no condition about which so much discussion occurs. Nevertheless, it seems that there is no disease in which the immunologic state is more important in the determination of the course and morphology of the lesions. We are fortunate in having in the English literature a discussion of the entire subject in a brief form by a man who is a master in this field, Joseph Jadassohn. In the *British Journal of Dermatology*, of 1929, there is an article entitled "Remarks on Tuberculin in Dermatology" (**41**:451 [Dec.]) which discusses these problems and in the ARCHIVES OF DERMATOLOGY, of 1930, there are articles by Professor Jadassohn entitled "Importance of Immune Biologic Processes in the Morphology of Skin Lesions" (**21**:355 [March]) and "Hematogenous Infectious Diseases of the Skin" (**21**:526 [April]).

It is seen from what Dr. Michelson said that immunology plays a great part in the study of tuberculosis of the skin. This study is based on tuberculin to a great degree. It is astonishing that in spite of the great number of sources of error, we can still obtain from tuberculin tests such accurate pictures of the actual immunology of tuberculosis of the skin.

The main sources of error in the reaction to tuberculin are these: First, tuberculin is an amorphous agent, and the active factor is not known, so many substances are injected which may give pseudoreactions. We are gradually overcoming this by purifying the tuberculin. The other causes of error are that, as a rule, the skin is not tested at the right time or in the right place. The skin is tested in a place which may not have the same immunologic status as the site of the actual tuberculous lesions. Furthermore, the tests are always made late, for the injection is given after the lesion has appeared. The state of the skin in respect to tuberculin immunology at the time of production and at the site of the lesion is what is really important. The Moro test at least overcomes the factor of testing the wrong place. The proper thing would be to test the site at which the lesion is about to appear, and that is at present obviously impossible.

The one thing I wish to stress is that in tuberculosis is found an example of what I think is a general and important immunologic rule. The tuberculodermas and tuberculin tests show that a state of active immunity is generally reached by

passing through a state of hypersensitivity (Sulzberger and Wise: Tuberculin: Newer Dermatological Considerations and Reasons for Its More General Use in Diagnosis, M. Clin. North America **14**:1555 [May] 1931). Hypersensitivity is a station on the road to immunity.

Dr. Michael H. Ebert, Chicago: I had an opportunity to see the woman whose picture was shown on the screen last, illustrating the primary complex in tuberculosis. I think her case illustrates excellently the immunobiologic principles stated by Dr. Michelson and emphasized by Dr. Sulzberger. Lewandowsky has shown that the type of reaction of the tissue to the tubercle bacillus depends on whether the animal has been previously infected or not. The condition in this girl was analogous to that of a patient infected for the first time with Spirochaeta pallida. In fact, her primary lesion so closely resembled a chancre that repeated dark-field examinations were made before we could convince ourselves that it was not a primary syphilitic lesion. The satellite bubo was also present. The picture does not bring out clearly the marked enlargement of the submaxillary lymphatic gland. Such a primary complex is well known to occur in the lungs of infants with associated peribronchial adenopathy. In this case after several weeks the lesion changed till it resembled lupus vulgaris, illustrating the change in the type of reaction of the tissue with the persistence of the infection.

Dr. Henry E. Michelson, Minneapolis: Dr. Sulzberger, undoubtedly, would have discussed the transition from allergy to anergy had time permitted. As he has emphasized previously in his writings, hyperallergy is found just before anergy. For example, erythema induratum histologically is closely related to the sarcoids, and in Bazin's disease there is a state of hyperallergy, while in sarcoid there is nearly always an absolute anergy.

Dr. Ebert discussed the case of a primary tuberculous complex of the skin. This condition has been known for a good many years, but has been recently emphasized by Bruusgaard. We must point out that tuberculosis verrucosa cutis is frequently associated with a tuberculous lymphangitis and adenitis and that a primary complex may become verrucous; hence the two conditions may be easily confused. However, there is a decided difference in the biologic aspects. The primary complex may be compared to a chancre, for it is presumed that the subject has received a primary infection. In the cases of tuberculous chancre the acute phase may pass, and a lupus-like lesion may replace the original ulcer or node.

EPITHELIOMA OF THE EAR

A CONSIDERATION OF THE DIFFICULTIES IN ITS TREATMENT WITH RADIATION

C. F. LEHMANN, M.D.
SAN ANTONIO, TEXAS

Cure of epithelioma of the auricle can always be accomplished by removal of the auricle. The chief object in treating the condition with radiation (radium and roentgen rays) is to obviate mutilation and accomplish cure with a good cosmetic result. If a satisfactory cure cannot be gained with radiation, no compromise short of radical treatment should be adopted. The advantages of treatment by radiation justify its use in nearly every case, unless indications point definitely to futility. Many epitheliomas on the auricle are easily cured, but there is a certain percentage of them that gives difficulty.

Hintze [1] stated that when the lesion is superficial and has not invaded cartilage the usual doses of radiation produce no injury to the cartilage, but when the cartilage itself presents a raw surface and is involved by extension of the epithelioma, the prognosis is bad; also, that if cartilage is treated with large doses of radium, there may be produced a painful and resistant ulcer. Pfahler [2] made the statement that if epithelioma is confined to the skin, it may be treated by electrocoagulation and radium or roentgen rays with practically certain cure, but that if the disease has invaded cartilage, radium alone will usually fail. Eller and Fox [3] recently published similar experiences.

This paper is concerned with the factors explaining the difficulties in treatment and the limitations of radiation therapy of the ear.

It is commonly supposed that cartilage is easily destroyed by radiation, and this is given as one reason why irradiation of cancer of the ear has limitations below the doses applied to other parts. This is partly true. Yet a comparison of the effects of radium on other cartilages with its effects on the cartilage of the ear shows that there is not such a vulnerability as is commonly supposed. Epithelioma of the eyelid responds satisfactorily to a dosage of filtered radium, varying from

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Read at the Fifty-Sixth Annual Meeting of the American Dermatological Association, Inc., Chicago, June 9, 1933.

Figures 2 and 6 have been omitted, owing to lack of space, but will appear in the transactions and in the author's reprints.

1. Hintze, A.: Strahlentherapie **17**:175, 1924.

2. Pfahler, G. E.: Electrocoagulation and Radiation Therapy in Malignant Diseases of the Ear, Nose and Throat, J. A. M. A. **85**:344 (Aug. 1) 1925.

3. Eller, J. J., and Fox, E. C.: New York State J. Med. **30**:1344 (Nov. 15) 1930.

80 to 150 mg. hours per square centimeter (or more) without damage to the tarsal plate. Likewise, a similar comparison can be made with epithelioma of the nasal alae. Any one who has had any experience in treating epithelioma of the auricle has seen good results from the use of a lethal cancer cell dose of radiation without any gross damage or later breaking down of the cartilage. And, conversely, he has probably seen also a breaking down of the tissue which continued as more radiation was applied. While I admit that cartilage may be damaged by a large cancer cell dose of radiation, I do not believe that the explanation of the failures in the radiation treatment is solely "vulnerability of cartilage." Certainly normal cartilage can withstand doses that are lethal to most epitheliomas.

In comparing the effects of radium on cancers over different cartilages, it is, of course, taken into consideration that the types of cancers vary, and therefore to attain cures technics necessarily have to vary according to the resistance of the cell; i. e., some grade 1 prickle cell growths are as resistant as normal skin. Those occurring on the nose and eyelid are practically all of the basal cell (or Krompecher) type, which are very susceptible to the action of radiation. Broders,[4] in a study of sixty-three cases of epithelioma of the ear, analyzed them into 61.9 per cent squamous cell type, 33.33 per cent basal cell type and 4.76 per cent melanotic squamous cell type; of the squamous cell type, 5+ per cent were grade 1, 66+ per cent grade 2, 23 per cent grade 3 and 5 per cent grade 4.

In an instance in which the cancer is extremely radiation-resistant, the lethal dose required may be harmful to normal structures. In such a case deficient treatment would be followed by extension of the cancer, and sufficient treatment would be followed by a caustic effect which is no more selective than the actual cautery or a cancer paste, thus defeating the object of radiation therapy, i. e., cure with good cosmetic result. It is fortunate that, with few exceptions, epitheliomas on the auricle are amenable to safe doses of radiation. Technic counts for much in treatment, and also explains the difference between good and bad results.

In analyzing this problem, I think that one has to consider along with the necessary amount of dosage needed for the cancer cell the amount or technic best suited to normal structures. Then when these two points are defined, another question must be settled, that of the histology of cancers involving the auricle and of the "cancer bed."

HISTOLOGY

The literature, in both textbooks and journals, on the histology of cancer of the auricle is very scanty. Hubler,[5] in 1924, reported a series

4. Broders, A. C.: S. Clin. North America **1**:1401 (Oct.) 1921.
5. Hubler, C.: Arch. f. klin. Chir. **132**:60, 1924.

of studies on this subject, and he quoted the work of a few others. These and those of Eibach, who likewise has studied cartilage epitheliomas in detail, do not agree absolutely. Eibach described the primary stage in which cancer invades perichondrium, as follows: "The perichondrium responds with proliferation completely like connective tissue. There is hardly anything left of perichondrium; one finds great increase

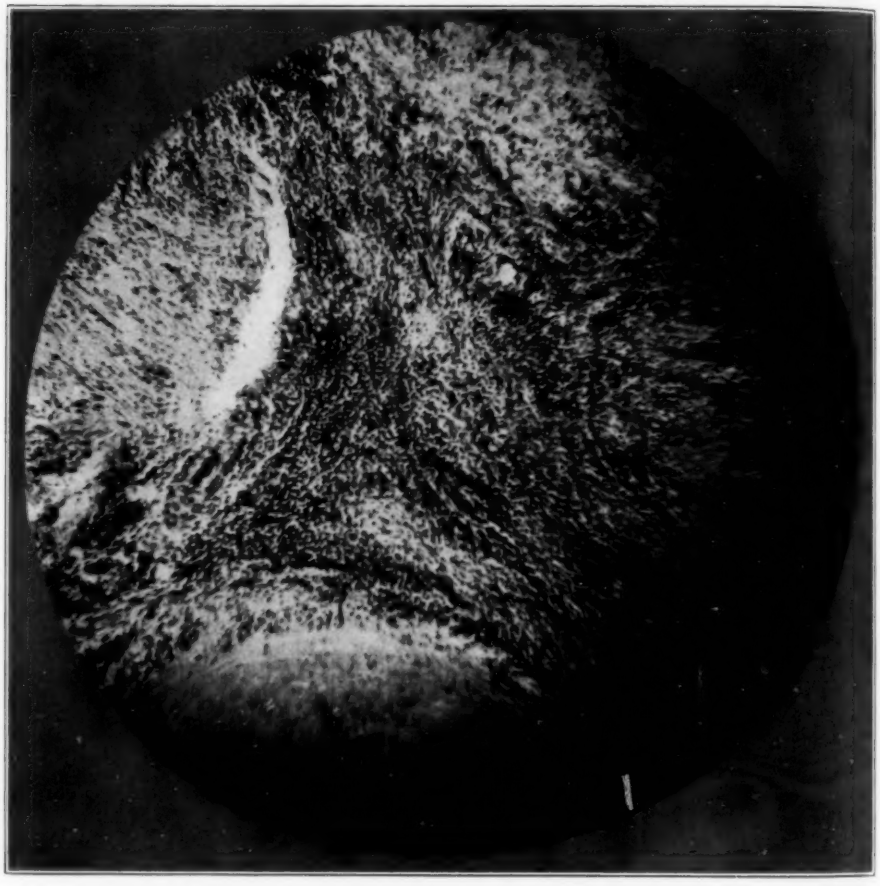

Fig. 1.—Round cells destroying the perichondrium.

in cell nuclei, which have lost the connective tissue characteristic and assumed that of round cells. This results in the separation of perichondrium from cartilage and the cartilage becomes frayed." Preceding the cancer cones, he stated, there "always is a zone of round cell infiltration, and then a deep-red staining band (von Giesen stain) which merges directly with the perichondrium, and later a zone of pale-staining, protoplasmic rich connective tissue cells which bind the cartilage in addition

to their relation to the perichondrium." He concluded that cancer cannot destroy the perichondrium but produces proliferation only, and after this it becomes destroyed. He described the destruction of cartilage by cancer as occurring after the cancer changes and weakens the cartilaginous ground substance and changes it into an undifferentiated substance suitable for cancer growth. He ascribed the dissolution of the cartilaginous ground substance to carcinomatous perichondritis. Eibach stated further that there is no dissolving power of cancer on cartilage.

Hubler contradicted Eibach, stating that he did not believe the cancer causes a proliferation of the perichondrium, and that cancer does not destroy perichondrium by pressure. He described also a wide zone of small cell infiltration, preceding the carcinoma, composed in part of round cells and in part of young spindle cells. These, he said, push in between the fibers of the perichondrium and between the perichondrium and the cartilage, and by their destructive action on the perichondrium and the cartilage matrix, "prepare the bed for cancer" (fig. 1). If the preceding cellular infiltration is milder, which appears noticeable in different cancers, then the cancer cones directly invade the spaces of the perichondrium and subperichondrium, but do not choose cartilage first. Cancer follows where the round cells have injured the perichondrium or the cartilage. Hubler mentioned, in support of this, a specimen of costal cartilage in which the perichondrium had not been pushed ahead by the cancer, but was in part completely destroyed and in part pushed aside by the invading cancer. Here there was an extraordinarily mild cellular infiltration preceding the carcinoma. Hubler, quoting Albrecht, said that "the bed is not sufficiently prepared," and he found that the cartilage is little injured by cancer while the surrounding tissue is already totally invaded by carcinoma. Hubler also mentioned the disagreement among different writers as to the meaning of the cellular infiltration. For instance, he mentioned Schiedal, Schmidt and Benke as showing that young fibroblasts are the factors which serve to stop the progressive growth of cancer. He also mentioned that Ribbert maintains that cellular infiltration in the neighborhood of malignant tumors accelerates the tumor growth, while von Bartkiewicz can show quite strong cellular infiltration in benign tumors. He said that the greatest truth is in the observation of Hausmann, who considers the small cell infiltration as the result of the inflammation which originates from the tumor and signifies a battle which the connective tissue wages against the invading swollen areas. Hubler himself found that where the infiltration is milder, the cartilage is destroyed in lesser degree, and he therefore concluded that the infiltration itself influences the destruction and is an expression of the strength of the cancer invasion.

Hubler made another interesting observation:

> . . . in pus-formation, the cartilage cells soon become necrosed, while the matrix, although in part changed, bears up for a long time; while in cancer invasion this is reversed. In this case, the fact that the cartilage cells and capsules retain their structure longest, and show complete staining while the matrix is completely invaded by cancer, proves that perhaps the physical chemical character of the cells is such that it is opposed to destruction by the secretions of carcinoma.

These observations are of extremely practical value, for they explain the progressive destruction of cartilage after an infected cancer of the auricle has been thoroughly irradiated. The explanation is that the infection, not being controlled by irradiation, keeps destroying cartilage. This observation is of extreme value in deciding on treatment. It is my opinion, and I think it is amply justified by Hubler's findings, that the outcome of an infected, and that of a noninfected, cancerous cartilage of the ear are very different, every other factor being equal. In other words, the presence of infection renders conservative treatment with radium doubtful (a point discussed in a previous paper by Pipkin and me[6]).

TECHNIC

Most of the epitheliomas of the ear are susceptible to the action of radium, though as a rule this group of epitheliomas are more resistant than those over cartilage in other areas. Hence, larger doses of radium are necessary. The following questions would immediately arise: If one is dealing with a very resistant epithelioma, would the dosage necessary to be lethal approximate the dose necessary to damage cartilage? In this event nothing would be accomplished, because the radium would produce more destruction of cartilage, owing to atrophy following its use, and would only promote rather than hinder the cancer's work. How tolerant of radium is cartilage? In considering this question it is to be remembered that it is being limited to the cartilage of the ear, because anatomic factors no doubt have some bearing on the effect. For instance, there is no subcutaneous tissue between the skin and the cartilage on the concha side of the auricle, and therefore there is no filtration of the radium dosage by intervening tissue, except by the very thin skin. This would apply to the use of beta rays, but not to that of the homogeneous gamma rays. The tolerance of cartilage for radiation means the tolerance of perichondrium (its nutrient membrane) for radiation.

These questions are answered in part by the following consideration of technic.

A marked difference is seen in the reaction of tissue to beta and gamma rays. The work of Dominici, Regaud[7] and others has made

6. Lehmann, C. F., and Pipkin, J. L.: Treatment of Epithelioma Adjacent to Bone and Cartilage, to be published.

7. Regaud, C.: Am. J. Roentgenol. **12**:97 (Aug.) 1924.

clear the advantage of filtered radium treatments, showing that there is less harm done the more radioresistant elements of tissue, such as blood vessels and fibrous tissue, with a more selective action on cancer cells. Regarding this, Regaud said:

> When one compares the effects produced by highly filtered X-rays of greater and greater penetration, or better, the effects of the most penetrating gamma rays of radium, one observes a phenomenon, discovered by Nogier and myself, of the greatest importance. As the radiation becomes more penetrating, the diffuse necrotizing effects diminish, then practically disappear, and finally only the selective effects remain which are manifested in the most radio-sensitive cells.

In commenting on this comparison of effects of beta rays and gamma rays on tissue Cade [8] stated:

> The study of the action of radon has shown that B rays caused necrosis of the tissues in the vicinity of the focus of irradiation. The necrosis is in inverse proportion with the screenage. The poorer the screenage the greater the destruction. The field of tissue destroyed never extends beyond 8 mm. from the center of irradiation. When non-filtered radon is used, it becomes evident that the B rays are non-selective in their action and affect normal and malignant tissue in nearly equal degree, the result being radium necrosis; .5 mm. platinum screens of B rays and the X-rays having a selective action on cancerous cells, necrosis is eliminated while destruction of malignant cells is still obtained.

Kennedy [9] maintained that by the adoption of the proper technic the difficulty of cartilage destruction in treating epithelioma adjacent to cartilage with radium can be overcome. He advocated the use of gamma rays, using for a filter 0.5 mm. of silver, 1 mm. of brass, 1 mm. of lead and 2 mm. of soft rubber. He gives 400 mg. hours as the total average dose. His results are very good and are obtained with no damage to the underlying cartilage.

EXPERIMENTS

With the object of comparing the effects of beta radiation with those of gamma radiation on cartilage, experiments were made on rabbit's ears. Beta rays were applied, a full strength plaque (2 by 2 cm.) being used with filtration of 0.1 mm. of almuminum and thin rubber, in direct contact for one and one-half hours. This is a dose that is ordinarily applied to an epithelioma. Gamma rays were applied by using in a brass capsule of 1 mm. thickness, covered with 1 mm. rubber, the following radium containers: (1) a silver tube, 25 mg.; (2) three platinum-iridium needles; 10 mg. each; (3) two steel alloy needles, 10 mg. each (total 75 mg.). This was applied at a distance of 1 cm. on gauze. The dose, which is usually given an epithelioma (except very resistant ones), 450 mg. hours, was used.

The same area of the ear was treated in every instance except as otherwise mentioned. The tissue was stained with hematoxylin and eosin.

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8. Cade, S.: Radium Treatment of Cancer, New York, William Wood & Company, 1929, p. 5.

9. Kennedy, W. H.: Radiology **7**:249 (Sept.) 1926.

COMPARISONS OF THE RESULTS WITH LETHAL CANCER CELL DOSES OF BETA AND GAMMA RAYS

Early Changes.—(*a*) Gross: Epilation, denudation and crusting occurred in two weeks.

With gamma radiation no changes that would photograph were seen, except for a faint erythema and a small amount of epilation (which was not permanent).

(*b*) Histologic: Sections were made two weeks after the radium was applied.

With beta radiation, the epithelium was of normal thickness but scaling. There was engorgement of the blood vessels of the cutis, the walls of which were thickened. The cartilage cells were distorted, and their walls were thinned. There was a cellular infiltration in the cutis. The perichondrium was thinned.

With gamma radiation, there was apparently no change in the epithelium. The vessels were not engorged. There was a fibroblastic reaction (hyalinization). The perichondrium was thickened. There was some distortion of the cartilage cells, though less than in the cartilage irradiated with the beta rays. In small areas the matrix was thinned to a one or two cell depth, and at these areas the cells stained very lightly and had thin walls.

Late Changes.—(*a*) Gross: With beta radiation, four months after the plaque treatment, there was alopecia on the thin scarred skin.

With gamma radiation, after the same length of time, the skin looked normal and was covered with a normal amount of hair.

(*b*) Histologic: With beta radiation, the epithelium was atrophied, and no epidermal appendages were seen. Blood vessels were very scanty. The perichondrium was extremely thin. The cartilage cells were extremely distorted. In places the cells stained dimly and were markedly diminished in number; in other places, which represented areas where blood and lymph spaces were present, the cartilage was repaired.

With gamma radiation, skin appendages and vessels were present. There was a normal appearance of the cutis. The perichondrium was thinner than normal. While the matrix was thinner, the cells stained more normally, as there was not the excessive basic staining seen in the early reaction.

OTHER COMPARISONS

Steel and Platinum Filtration.—Two steel needles were applied directly to an ear and two platinum needles were applied directly to a similar area of another ear. The radium content of the two types of needles is practically the same. With the steel needles, the length of time in which an erythema appears on human skin is from one to one

and a half hours. With the platinum needles, two and one-half hours are necessary to produce an equivalent reaction. Nine months later sections were made of these ears. The area treated with steel needles (which allow more beta radiation) showed pronounced atrophy of the skin and its appendages, scanty blood vessels of the cutis and a very thin perichondrium and cartilage (fig. 3 *A*). There was almost a total absence of any intercellular substance in the cartilage. The area treated with platinum needles (which yields much fewer beta rays than the steel needles) showed absence of epidermal appendages and areas of frayed cartilage which represented destruction, probably due to an early endarteritis (fig. 3*B*). But the cartilage compared better with the normal, as a distinct perichondrium was seen and the cells were not so distorted and showed intercellular substance.

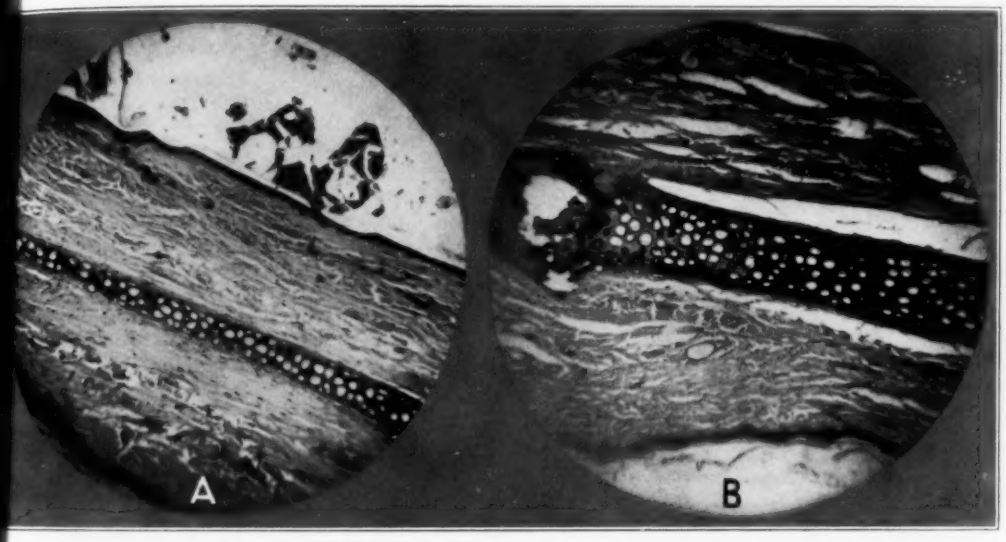

Fig. 3.—*A*, nine months after beta irradiation; *B*, nine months after gamma irradiation.

Larger Dose of Gamma Rays.—A dose of 1,050 mg. hours of gamma rays was applied to an ear. In three weeks there were no gross changes in the skin. Section showed the epidermis to be normal and epidermal appendages present. There was a cellular infiltration of the cutis with thickening of the walls of the vessel. The cartilage was thinned as was the perichondrium. The cartilage cells were distorted and packed together tightly, there having occurred a loss of the intracellular substance. Some places showed a destruction of cartilage comparable to that seen in the early effect of 450 mg. hours.

Five months later the gross appearance was alopecia and atrophy.

Section showed the cartilage repaired and as thick as, or thicker than, normal. There was a hyperplastic perichondritis. There was increased fibrous tissue of the cutis, the walls of the vessels of which were much thicker than normal. The epidermis, though intact, was atrophied and had few appendages.

Comment.—(It was desired in this experimental work to compare the effect of both beta and gamma rays on infected as well as on noninfected ears. Various organisms and aleuronat were injected, all of which caused an abscess. But the abscesses healed too quickly, and I was unsuccessful in producing a chronic perichondritis.)

These histologic changes corroborate the clinical observation that tissue withstands lethal cancer cell doses of gamma rays better than the

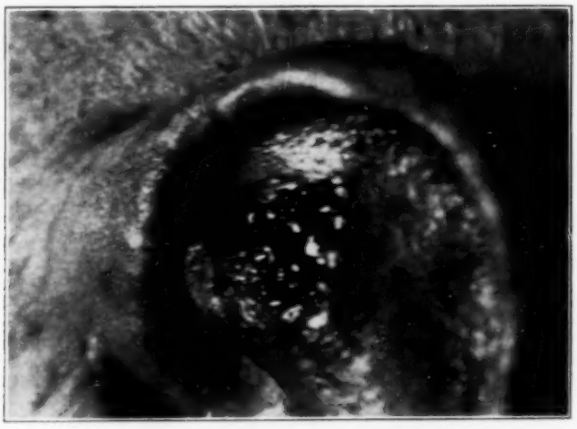

Fig. 4.—Basal cell cancer complicated with infection. Cure was obtained with 450 mg. hours of radium (gamma).

equivalent doses of beta rays. It was seen that the tissue recovered better from the gamma doses. Early effects of gamma rays are thickening blood vessels and thickened perichondrium. Following this a thinned perichondrium and matrix are noted. Nine months later the matrix and perichondrium approach the normal; the blood vessels are still evident in the cutis. The skin appendages can be destroyed, but large doses are necessary to accomplish this. Beta rays produce an inflammatory reaction which is followed by atrophy of the matrix, perichondrium, blood vessels and skin, of which no repair, or very little, is made.

A rabbit's ear is vascularized better than a human ear. It contains, relatively, a much greater amount of cutis, through which course lymph and blood. Healing and restoration of damaged tissue are very prompt. Therefore, these comparisons are very applicable to the question of dosage and technic in the treatment of the human ear.

COMMENT

In the light of the foregoing statements regarding the histology of epithelioma of the cartilage and the technic of treatment, it can be seen that the treatment cannot be standardized to fit every case. All of the factors which have been presented have to be considered before deciding on the type of treatment. A small basal cell epithelioma on the skin, not attached to the cartilage, can be satisfactorily treated with beta rays shielded close around the epithelioma. If infection complicates the epithelioma, the success is rendered more uncertain; but nevertheless it would be best to use gamma radiation (whether the lesion is of basal

Fig. 5.—Cartilage invaded by basal cell cancer and infection. Irradiation was futile.

cell type or not, fig. 4). If the cartilage is already invaded, irradiation is futile (fig. 5). If the epithelioma is not a basal cell but a prickle cell type, it will require a heavy dose of radiation. Beta rays should not be selected for it, bacause of the danger of irreparably damaging the perichondrium, and therefore gamma rays should be used. The effect of previous treatment has to be taken into consideration at times. For instance, in a recurrence of an epithelioma that has been treated before with soft radiation (roentgen rays or beta rays of radium), one would consider how much the perichondrium is damaged. If there is not marked atrophy of the skin, one could well apply further radiation with gamma rays. If there is evidence that the perichondrium is broken, the efficacy of further radium treatment is very doubtful.

CONCLUSIONS

From the foregoing considerations, I feel that the following conclusions can be drawn:

1. The ordinary smaller doses of radiation that will cure the smaller basal cell epithelioma do no irreparable damage to cartilage.

2. If infection is present to a marked degree, it mitigates against cure of the cancer by radiation. If radiation is used in the face of it, gamma rays are the method of choice, for the effect of beta rays on cartilage is similar to that of the infection.

3. If one has a radiation-resistant epithelioma, it is best to use gamma radiation.

4. If one is treating a cancer that has recurred after soft radiation, it is best to use gamma rays of radium.

DISCUSSION

DR. E. P. ZEISLER, Chicago: Dr. Lehmann has given us an interesting and instructive demonstration of the effect of radium on cartilage. We are all interested in the treatment of epithelioma about the ear, and I should like to show two or three slides to illustrate my experience with a few cases (presented slides).

The first case was a large squamous cell carcinoma developing in the scar of a lupus erythematosus. The epithelioma had been treated with roentgen rays and radium, and we strongly suspected that we were dealing with a highly resistant type of carcinoma. The patient was advised to have a surgical removal. At this time, a removal of part of the ear would have sufficed. Instead of this she went to a radium therapeutist who treated her for three months with radium therapy. This man has at his disposal several grams of radium, so there is no question about the technic. The second slide shows the rapid growth of the carcinoma under this treatment. It was necessary to remove the entire ear by electrosurgery and surgical diathermy. I am told that the patient is making a good recovery.

The second case illustrates the excellent results that can be obtained in an early nodular epithelioma of the rim of the ear by preliminary destruction with the electric cautery followed by treatment with relatively small amounts of radium, which most dermatologists have at their disposal.

In my experience, the use of radium should be limited to those cases of epithelioma in which the cartilage is not involved.

DR. HOWARD MORROW, San Francisco: I think it is rather difficult to make a positive diagnosis of an early basal cell epithelioma of the ear. Dr. Lehmann's statistics show an incidence of basal cell epithelioma of the ear of roughly 30 per cent, which is entirely too high. I think that it is closer to 15 per cent, and these early cases are the ideal ones for radium therapy.

Some years ago we reported on early cases of carcinoma of the ear treated with radium, and we thought our results were good. We used plaques, glass seeds and gold seeds, and we got equally good results from all three. Of course, the advantage of the gold seeds is that the reaction is very small.

In the last four or five years I doubt if we have used radium in more than three or four cases, for the reason that we now think the best treatment is a thorough curetting followed by electrodesiccation.

DR. HAROLD N. COLE, Cleveland: I should like to subscribe to the remarks of Dr. Morrow regarding the value of endothermy and curettage in lesions of the ear. Otherwise, one is apt to get recurrences, and, as already stated, with these recurrences there is probably a certain amount of damage from radiation already, so that if one attempts to use further radiation measures one is sure to have bad results. I think that one can get good results with the implantation of platinum needles, leaving them in for a week or ten days. It is surprising how little reaction ensues. In certain cases we have used these platinum needles, but in the main we depend on endothermy and curettage.

DR. EARL D. OSBORNE, Buffalo: I also wish to subscribe to what Dr. Morrow said about the use of radium in the treatment of epitheliomas on the ear. I live in a city where there is an institution which has a very large amount of radium. In the last few years, I have seen several patients who died of metastases following the use of large amounts of radium, only the gamma rays being used. In my opinion, these growths are better treated with endothermy, and I believe the percentage of cures is higher than with any form of radiation. I believe the cosmetic appearance should be secondary in importance to the cure of the patient.

DR. C. FRED LEHMANN, San Antonio, Texas: This paper deals strictly with the limitations of radium therapy. Certainly the cosmetic appearance is secondary. However, if one uses radiation and recognizes its limitations, good results can be obtained.

I was glad to hear of the experience with the use of the electric cautery. Certainly cosmetic consideration is at times a factor, particularly if a doctor has epithelioma of the ear. I have had that experience.

The chief point I think is that if radiation is used and a prompt cure does not result, the treatment should be discontinued and the ear removed.

With regard to the use of highly filtered radium, I wish to call attention to a point which I think is becoming generally recognized. If one uses heavy radiation according to Regaud's technic once, it should not be continued, for two or three months after its second use a plug of tissue is apt to drop out.

DERMATITIS VEGETANS

REPORT OF AN EXTENSIVE CASE

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Dermatitis vegetans cannot be accepted as a clinical entity since it occurs as a secondary manifestation in unrelated dermatoses of both benign and grave character, indicating a varied etiology. Our problem, therefore, consists in separating these various conditions, especially from the standpoint of etiology and prognosis.

Hallopeau described a benign type beginning as small erythematous circular patches; millet seed-sized seropustules developed, the lesions enlarging by peripheral extension as they cleared in the center, leaving a brownish pigmentation. The case here reported (case 3) corresponded to his description in clinical detail.

REPORT OF CASE

M. L., a man, aged 80, was admitted to the Newark City Hospital in June, 1929.

Physical examination and the general laboratory examination revealed nothing unusual.

The cutaneous lesion at this time consisted of a vegetating dermatitis limited to the groins and perineum. Under treatment with antiseptic wet dressings, the patient improved and was discharged in November, 1929, at which time no active lesions were apparent.

In November, 1932 (three years later), he was again admitted to the hospital presenting an eruption that involved almost the entire surface of the skin, with the history that he had remained free from eruption for about a year, when he had a recurrence in the original site of involvement, which gradually extended peripherally from both groins outward and downward over the thighs to the inner sides of the knees, circling anteriorly and posteriorly over the upper two thirds of the legs; spreading upward, it involved the entire abdominal surface to the sternal region, forming irregular curved raised lines across the lower part of the chest.

Posteriorly, it spread through the crural fold, outward over the buttocks and upward over the lumbar and dorsal regions, leaving only 2 or 3 inches (5 or 7.6 cm.) of normal skin between the anterior and posterior lesions. Separate foci had developed in both axillae, spreading downward over the sides of the chest almost to the border of the ascending lesions. Separate foci involved the right nipple, soles and dorsal surfaces of the feet and left elbow. The face, scalp and hands remained free from eruption. Within the area traversed lesions persisted, making double tortuous ridges almost throughout the entire distribution.

Read at the Fifty-Sixth Annual Meeting of the American Dermatological Association, Inc., Chicago, June 8, 1933.

Under observation new foci developed both within and outside the affected areas, beginning as pea-sized or dime-sized, slightly raised erythematous lesions; closely set millet seed-sized seropustules developed, the lesions advancing peripherally and subsiding centrally to produce variously sized circinate lesions or curved segments. As the borders advanced, the pustular element subsided, leaving elevated

Patient with dermatitis vegetans.

grayish ridges, consisting of closely set, keratotic, conical papules, which gradually flattened toward the inner aspect of the lesion as they disappeared, leaving a deep brownish, almost black pigmentation, which persisted, making a striking picture in contrast with the outstanding grayish ridges along the borders.

The only subjective symptom consisted of an intense pruritus, which was unusually severe, rendering the patient extremely nervous. He was almost exhausted and mentally despondent from continual scratching without relief.

Histologic Examination.—Paraffin sections and sections stained with Zenker's solution, hematoxylin and eosin, and Gram-Weigert and Brown-Breen stains were studied.

The surface was covered with an exudate consisting of polymorphonuclears, erythrocytes, fibrin, partly degenerated keratin and short cylindric bodies resembling hyphae. The malpighian layer was distorted and hyperplastic, contained numerous polymorphonuclears and pigment-laden macrophages and showed several circumscribed small abscesses and superficial ulcerations. Beneath this layer were seen numerous pigmented macrophages, some of large size. This pigment was dark brown and distinctly granular. The smaller vessels were congested, and lymphatic spaces were numerous. The pigment mentioned was a very prominent feature.

Direct examination with sodium hydroxide solution showed masses of interlacing hyphae, which could not be identified from these preparations alone.

Bacteriologic Examination.—Small pieces of skin were placed on Sabouraud's medium. After five days a fluffy, white growth was seen, resembling somewhat the initial growth of the trichophytons. Transfer was made to 4 per cent dextrose broth in hanging-drop cultures, Sabouraud's agar plates, Czapek agar plates and slide cultures of the Henrici type, Sabouraud's agar being used.

(*a*) Hanging-Drop Cultures: A slow growth without secondary colony formation developed. The hyphae were generally slender, septate, branching and without visible spores; after three weeks large flat spirals formed terminally on a few hyphae. No distinguishing elements were seen.

(*b*) Henrici Slide Cultures: The appearance was much the same as that seen in the hanging-drop cultures, but after six weeks' incubation numerous small black perithecia were formed. These were entangled in the mycelium, which showed large, flat, terminal spirals and an oidium-like appearance of the submerged hyphae. A perithecium broken open was seen to contain small, brown, oval spores. These were smooth, without tubercles or bars, some being wrinkled irregularly. They averaged from 4.5 to 3 microns to 3.1 to 2.4 microns in size. The wall of the perithecium, examined by cutting paraffin sections, was about 8 microns in thickness, consisting of a pseudoparenchymatous rind; no ostioles were observed.

(*c*) Sabouraud and Czapek Agar Plates: A rather slow, downy, white growth, circular and not wrinkled, with a small central knob developed. As the gross colony aged it became more tawny or light buff colored, and after about six weeks, scattered black perithecia appeared.

Identification.—The foregoing description corresponds to that given for Euascomycetes, of the order of Aspergillales and the family of Aspergillaceae, and is probably a species of Aphanoascus; it differs from the Gymnoascaceae in the formation of a definite pseudoparenchymatous rather than a plectenchymatous peridium. It is not claimed that this is the causative organism, although it may be. Other members of this family are both saprophytic and pathogenic for man.

Treatment.—Daily baths of cupric sulphate with sodium borate were given. The mixture consisted of 3 ounces (93.3 Gm.) of cupric sulphate and 9 ounces (279.9 Gm.) of sodium borate. One ounce of this preparation was added to each bath. Following the bath a 6 per cent ointment of salicylic acid was applied over the entire involved area. Gradual improvement followed, the lesions being controlled after several months of persistent treatment, but new lesions continued to develop both within and outside the lesions, over a period of about nine months. Treatment was then changed, the salicylic acid ointment being omitted and a dry

powder substituted consisting of 2 grains (0.13 Gm.) of cupric sulphate, 2 drachms (7.77 Gm.) of pulverized zinc oxide and 6 drachms (23.32 Gm.) of pulverized purified talc was applied after the copper baths. The attendant, wearing rubber gloves, applied the powder with firm friction, and in vesicular areas the vesicles were ruptured and the powder thoroughly rubbed in.

Rapid improvement followed; the newly developing lesions were readily controlled, the pruritus gradually subsided, and on March 16, 1933 (eight weeks later), the patient was discharged. No active lesions were present, and only the deep pigmentation remained, which was becoming lighter.

The outcome in the cases previously reported [1] is as follows: The patient in case 1 has been seen at various times since his discharge from the hospital and has remained free from eruption.

The patient in case 2 came under observation again in November, 1932 (three years following previous reports). His physical condition had remained unimpaired, and aside from the distress caused by his cutaneous condition, there were no symptoms of a constitutional character. Since he was last observed he had tried numerous plans of treatment including vaccines, injections and radiation therapy, and while he improved, the eruption being less extensive, he had never been entirely free from eruption at any time during this period. The involvement of the mucous membrane of the mouth which was present when he was last seen had entirely cleared up, and no recurrences had developed in this location during the past year. The locations involved at this time, which had never been free from eruption from the time of onset twelve years before, consisted of both axillae, the genitocrural region, soles and the area above the toes. The left great toe was inflamed, and a purulent discharge exuded from the nail bed.

A trial with copper treatment as outlined previously was advised and continued until May (a period of about six months) without any marked improvement, when it was discontinued. The patient is now under treatment with bacteriophage therapy.

Classification of this case is difficult, considered in relation to cases 1 and 3: There was a difference in the primary lesion which consisted of a pinhead-sized pustule or groups of pustules, while in cases 1 and 3 the onset consisted of a circinate erythema varying in size from that of a pea to that of a dime in which vesiculation preceded the pustulation. The laboratory findings were likewise negative for fungi on repeated examinations, only various bacteria, including Staphylococcus albus, Staphylococcus aureus and an unclassified microbacillus, being discovered.

Impetigo herpetiformis has been suggested as a possible diagnosis, but case 2 lacks the constitutional symptoms of this condition. What-

1. Wallhauser, H. J. F.: Dermatitis Vegetans: Report of Two Cases, Arch. Dermat. & Syph. **19**:77 (Jan.) 1929.

ever the outcome may be, this case cannot be included in the group described by Hallopeau in which cases 1 and 3 can be considered, as they agreed with his contentions both in clinical course and response to local antiseptic treatment. The ready response to dry cupric sulphate should establish a new feature in the management of these otherwise intractable cases. The finding of an organism not previously described in relation to this type of eruption should be considered, but will await further investigation in order to establish it as a possible etiologic factor in certain cases coming under the head of dermatitis vegetans of the Hallopeau type.

ACTINOMYCOSIS WITHOUT GRANULES

JOHN A. GAMMEL, M.D.
CLEVELAND

At the last meeting of the American Dermatological Association, Guy and Helmbold [1] reported on a rather unique condition termed "nocardiosis cutis gangraenosa." The authors expressed the opinion that nocardial infections of the skin are more frequent than the scant reports indicate. As the literature on this subject was most capably reviewed at that time, I wish to go in *medias res* and report on another type of infection caused by a closely related organism, but for reasons set forth here, I prefer the term "actinomycosis without granules."

REPORT OF CASE

History.—A 15 year old American boy was admitted to Lakeside Hospital on Feb. 3, 1931. His history was irrelevant except for the fact that he suffered from acne of the face and back. Three months prior to admission he noticed a small red papule on his back. It was not painful although slightly tender. He squeezed it frequently with his fingers and it grew slowly, becoming more and more painful. One month after onset he consulted a physician who opened it without getting any pus. At that time three other papules appeared on other parts of the body. He did not touch them, and they gradually became less painful. Since the onset the patient had lost 5 pounds (2.3 Kg.) in weight. He had no cough and no symptoms referable to his sight or mentality.

Physical Examination.—The pupils were small but equal, reacting promptly to light and in accommodation. The eyegrounds were normal. The tonsils were enlarged, with whitish exudate in the crypts. The right lower molar was carious. On the sides of the neck and in both groins, small lymph nodes were palpable.

The patient's skin was oily, and there were numerous comedones. The pores were large, especially on the face and midportion of the chest and between the shoulders. The forehead, cheeks and upper part of the back showed a moderate number of acne papules and pustules.

Special Examination.—On the right loin, close to the midline, about level with the ninth rib, was a rounded, slightly bluish, soft elevation about 7 cm. long, 3 cm. high and 5 cm. wide. The central part was ulcerating. From the base issued a moderate amount of mucopurulent discharge of a peculiar aromatic odor. The area was very tender to the touch. The skin over the remainder of the lesion was

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Read at the Fifty-Sixth Annual Meeting of the American Dermatological Association, Inc., Chicago, June 8, 1933.

From the Department of Dermatology and Syphilology of the Western Reserve University Medical School and of the Lakeside Hospital, Service of Dr. H. N. Cole.

1. Guy, W. H., and T. R. Helmbold: Nocardiasis Cutis Gangrenosa, Arch. Dermat. & Syph. **27**:224 (Feb.) 1933.

dull red and showed several violaceous pits, one of which broke down and was transformed into a draining sinus. A roentgenogram did not demonstrate any involvement of the bone. Small, crusted, erythematous tumors were seen also on the left wrist, on the side of the right thigh and over the right clavicle. The rest of the physical examination gave negative results.

Course.—As the first biopsy specimen suggested a tuberculous process, a filtered roentgen treatment was given on February 22, and daily exposures to the alpine lamp were ordered. While the tumor on the back flattened out, it, at the same time, spread. A second biopsy specimen and cultures taken on March 5 established the diagnosis of actinomycosis. Then 10 drops of a saturated solution of potassium iodide was given three times a day by mouth.

On March 14 the patient complained of general malaise, headache and stiffness of the neck. The left frontal sinus and the antrum were tender. Roentgenograms revealed increased density of both sinuses. During the next few days a right internal squint and double vision developed. The visual fields were not contracted, but on ophthalmoscopic examination the disks were found markedly engorged, the edges completely hidden and the cups obliterated. There were numerous white patches of exudate on the disks and running out into the surrounding retina. The disks were choked, about 3 diopters, and in the right eye there was an early star figure.

Cisternal Puncture.—The pressure was 540 mm. The Pandy test was strongly positive, and the cell count 4. The cultures were negative, but branching threads were found in the sediment. When the dosage of potassium iodide was diminished, the vomiting ceased. Compound solution of iodine was given intravenously, starting with 2.5 cc., the dose being increased 0.5 cc. every second day. Later ethyl iodide was given by inhalation; neoarsphenamine and sodium iodide were administered intravenously, and methenamine tetraiodide ($C_6H_{12}N_4I_4$) by mouth.

Subsequent Course.—In spite of all therapeutic efforts, the patient's condition grew continually worse, and his sight was failing rapidly. Early in April the engorgement of the disks had reached 5 diopters, and the visual fields showed a bilateral left-sided homonymous hemianopia. The boy was rather stuporous; he was frequently nauseated and vomited occasionally. The headache was undiminished, although liberal amounts of fluid were taken out by cisternal puncture every other day. The reflexes of the upper and lower extremities were about equal on the two sides. The lower extremities showed some increased muscle tonicity, more so in the left leg. There were readily elicited Babinski, Oppenheim and peroneal reflexes on the left side. There was no ankle clonus on either side. The sensibility was not greatly disturbed, but on the left foot the deep muscle sense was not quite normal. The Romberg sign was negative. The conclusion of the consulting neurologist was that the brain and spinal cord were involved by an encephalomyelitic process (Dr. Stone).

Late in April, the left-sided Babinski and Oppenheim reflexes had disappeared. There was a slight nystagmus to the left with a quick component to the right. The teeth ached, and the whole mouth "felt funny." The patient's memory was poor. Early in May the visual fields were greatly contracted, but the homonymous hemianopia and reflex changes could not be demonstrated for a short time. Nevertheless the patient's sight showed no improvement, and by the middle of May he was almost blind. Roentgenograms of the chest, spine and skull remained negative.

Dr. Elliot Carr Cutler, who had seen the patient several times in consultation, suspected a lesion in the right side of the brain and, on May 19, performed a

right subtemporal decompression. The dura was found extremely tight and thickened; a sclerosing process was gluing the pia, arachnoid and dura together. The brain was very dry and extremely tight. Where the sclerosed process was not old, there were opacities of more recent nature in the pia. The ventricles were apparently collapsed.

Following the operation the patient felt better; the temperature rose only once to 38.6 C. (101.5 F.), and he was able to sit up in a wheel chair. The wound healed per primam, but an ever enlarging hernia formed at the site of decompression. The intracranial pressure increased again, and eventually the patient could not even see light. The left side became paretic, and the extensors of the fingers of the left hand were paralyzed. Pain and sensitivity to touch were diminished on the left. The Babinski reflex was positive on the left.

On June 16, the patient became unconscious and cyanotic, and the respiration irregular. He died the same day at 6 p. m.

Laboratory Data.—The urine of the patient remained normal throughout. There were from 14,000 to 18,000 white blood cells and from 3,400,000 to 4,100,000 red blood cells, the higher number being reached during the last few weeks of life. The differential blood count follows: polymorphonuclear leukocytes from 78 to 89 per cent; small lymphocytes from 11 to 21 per cent; large lymphocytes and transitional cells, from 1 to 7 per cent; eosinophil leukocytes, from 0 to 3 per cent; basophil cells, from 0 to 1 per cent. A total of twenty-four cisternal punctures was performed. The pressure varied from 140 to 600 mm. There were from 1 to 4 lymphocytes present up to the time of operation; afterward, around 365, of which 95 per cent were lymphocytes and 5 per cent polymorphonuclear leukocytes. The Wassermann reaction was negative; one Lange test was 1112333000. The tuberculin reaction was positive, 1:1,000. The complement-fixation test for human and bovine tuberculosis was negative. Several blood cultures were negative.

Histologic Examination (Dr. Robert A. Moore, Institute of Pathology, Western Reserve University Medical School).—The first biopsy (February 3) showed a diffuse inflammation in the subcutaneous fibro-adipose tissue, characterized by extreme edema, slight fibroblastic proliferation and marked cellular infiltration. The predominant cells were the plasma cell and mononuclear leukocyte, although small lymphocytes and eosinophilic and neutrophilic polymorphonuclear leukocytes were present. Many of the mononuclear leukocytes showed phagocytic activity, in some instances of highly refractile acidophilic material. Young capillary sprouts were only moderately numerous. There were no areas of necrosis. There were localized areas of hemorrhage. There were a few large multinucleated cells but no definite granulomatous lesions. The media and intima of the medium-sized and small arteries showed edema and slight cellular infiltration with reduction in the size of the lumens. There was a moderate migration of polymorphonuclear leukocytes into the epidermis.

The stains for acid-fast bacilli gave negative results.

The second biopsy (February 5) showed the wall of a subcutaneous abscess formed by essentially the same type of inflammatory tissue. There were more fixed tissue proliferation and new capillary formation. Gram's stains showed throughout the granulation tissue a number of short mycelial fragments which often tapered off in a chain of coccoid sporelike bodies. Branching forms were common. The mycelial threads were gram-negative, and the sporelike bodies were gram-positive.

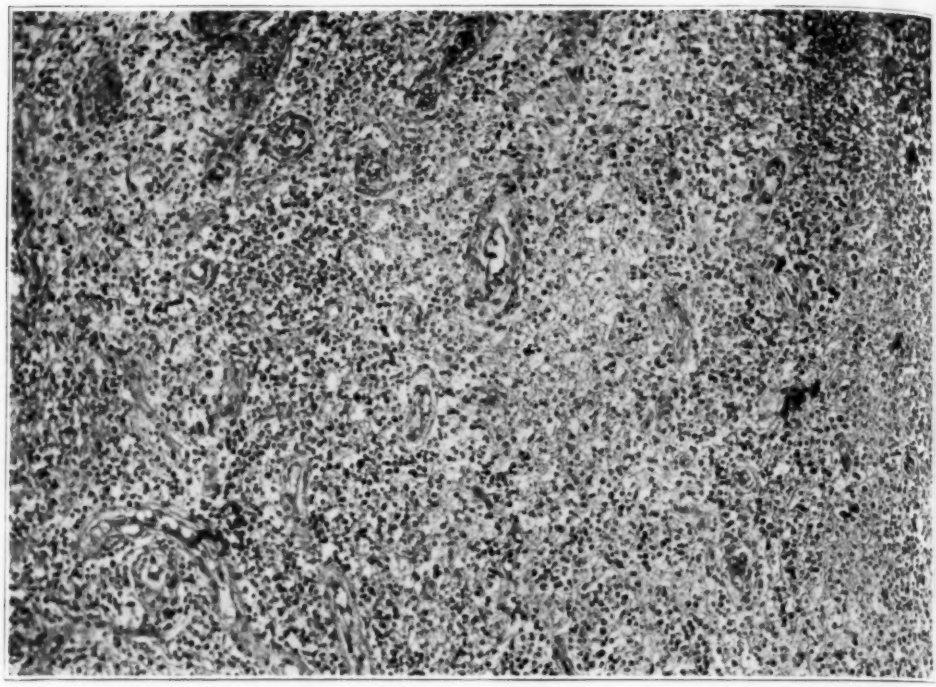

Fig. 1.—Low power photomicrograph of a typical area of inflammation. Note the marked edema and cellular infiltration with the extensive fibrin network and new blood vessel formation. Reduced from a magnification of × 120.

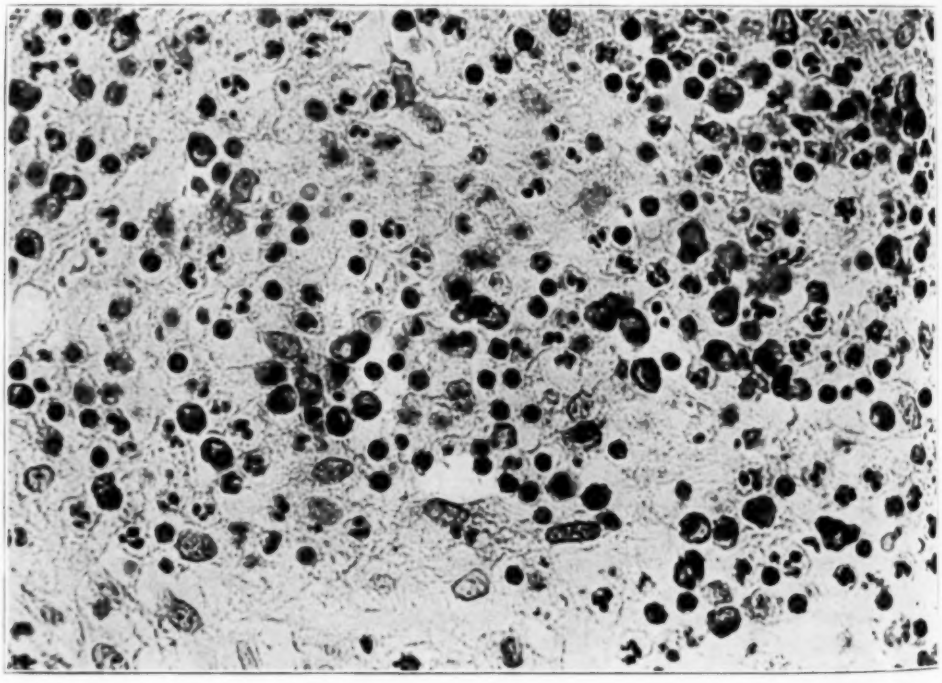

Fig. 2.—High power photomicrograph of the same area shown in figure 1 demonstrating the types of cells represented. Reduced from a magnification of × 270.

The third biopsy specimen (May 9) was similar to the second and showed the same granulation tissue as the wall of a deep, subcutaneous abscess.

The diagnosis was subcutaneous actinomycosis.

Mycologic Examination.—When the second biopsy was made on March 5, soft granulation tissue from the depth of the tumor was inoculated on routine mediums. In order to obtain material free from surface contamination, the specimen was

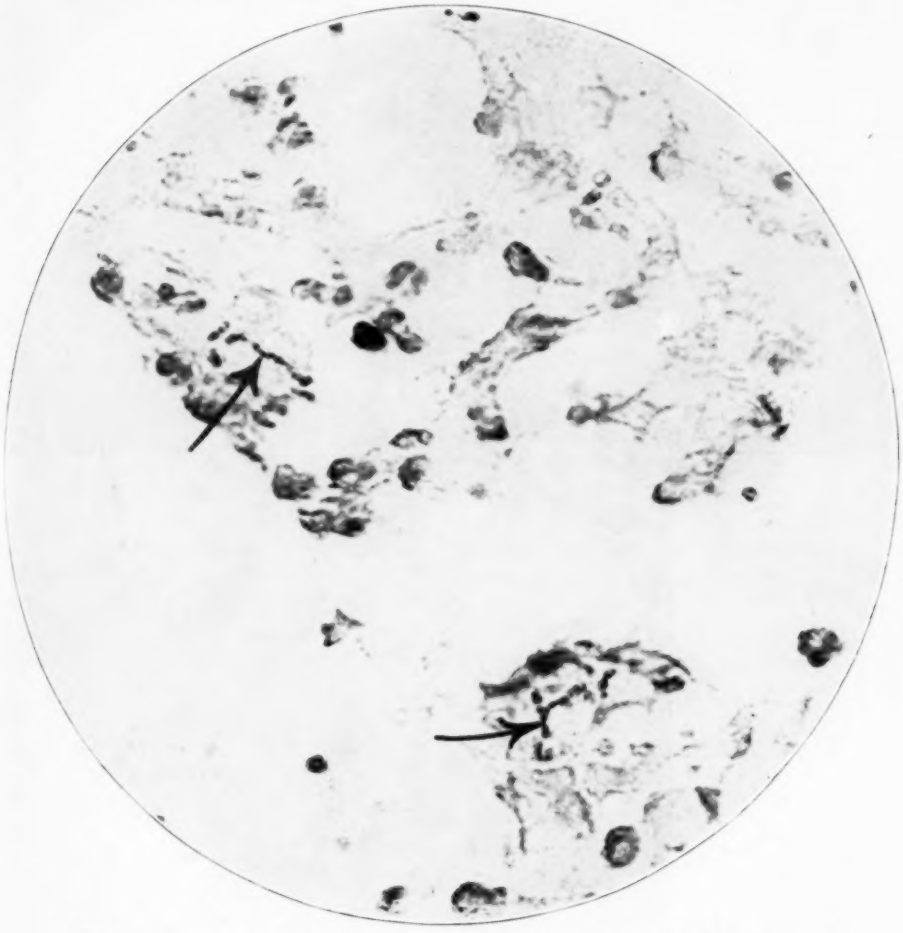

Fig. 3.—Granulation tissue with mycelial fragments. McCallum's stain; reduced from a magnification of × 1,940.

taken from a part of the tumor where the skin was intact. Within a few days a fine, white, powdery growth appeared on all points of inoculation; none of the culture tubes were contaminated. As the identity of the organisms seen in sections and in culture was suggested, the skin was punctured in various places in the periphery of the tumor, and a few droplets of bloody fluid were aspirated. A growth identical with the first resulted. Another biopsy late in March confirmed our previous histologic and cultural observations.

The fluid obtained at cisternal puncture was frequently examined, and fine threads and sporelike bodies suggesting invasion by the same organism were found thirteen times in the sediment, but all attempts at culture gave negative results. Fluid kept in the incubator for a month remained sterile. However, material from cultures inoculated into the patient's spinal fluid yielded luxurious growth.

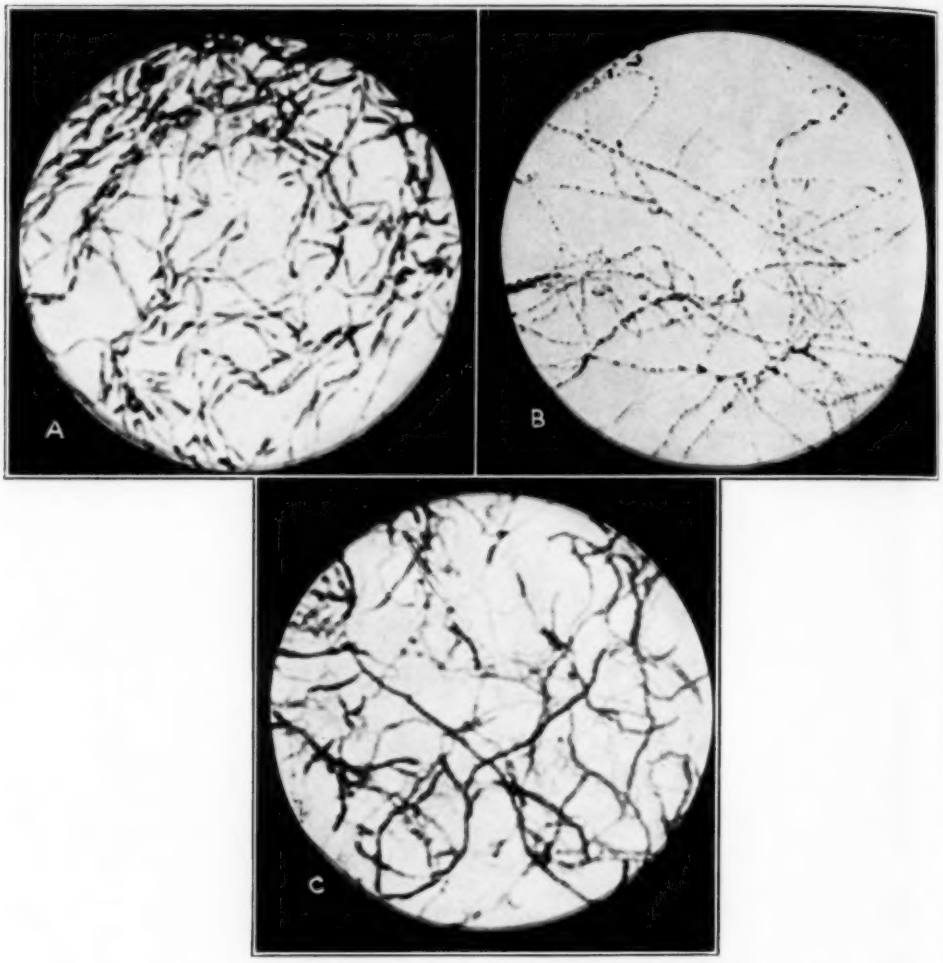

Fig. 4.—Hanging-drop cultures in Dunham's peptone broth. Reduced from a magnification of × 1,180. *A* shows Actinomyces asteroides; *B*, Actinomyces phenotolerans, and *C*, Actinomyces hominis.

A careful study of the cultures led to the conclusion that the organism, according to Bergey's "Manual of Determinative Bacteriology," belongs to the order Actinomycetales, the family Actinomycetaceae and the genus Actinomyces. The characteristics of the fungus did not fit any of the species hitherto known. Since the identification of Actinomycetes is difficult to the inexperienced, and as I did not want to increase the confusion in this field by the unwarranted creation of

new species, I submitted my findings and cultures to Prof. C. H. Werkman of the Iowa State College of Agricultural and Mechanical Arts. This well known authority on the subject of Actinomycetes concurred in my opinion and proposed to term the fungus "Actinomyces phenotolerans." As Professor Werkman has prepared a mycologic description of the organism for publication, I limit myself here to a definition summarizing our combined findings.

Actinomyces Phenotolerans (C. H. Werkman).—There was a straight, continuous mycelium with lateral branching. The diameter was less than 1 micron. There was abundant conidia formation by fragmentation. The aerial mycelium was short. There was spore formation of prostrate racemose type. No spirales were observed. The organism was acid-fast to a marked degree. The gram stain was amphophilic with gram-negative hyphae and gram-positive spores.

Krainsky's Dextrose Agar: Small, round, flat colonies formed which were tenaciously adherent to the medium. The surface was powdery, and white to grayish white with an orange hue in old cultures. The surrounding medium was not discolored and had no odor.

Starch Agar: No diastase formation was observed.

Gelatin: The gelatin liquefied very slowly, and there was a white surface growth.

Serum: There was a cream-colored surface growth with arborization.

Dunham's Peptone Broth: An abundant flaky growth was noted.

Litmus Milk: With this medium, there was an abundant surface growth, which became alkaline.

Potato: A luxurious growth of pinhead-sized, chalky colonies occurred, which later assumed an orange tinge and formed a confluent membrane. There was a market garden-soil odor.

Sugar Broth: There was a good growth in most sugars, with flaky colonies on the surface and on the bottom; it became alkaline.

Nitrates were reduced to nitrites.

There was a good growth in broth with 0.5 per cent phenol.

No tryosinase reaction and no soluble pigment formation were observed.

The organism was aerobic.

The optimal temperature was 37 C.

The organism is the cause of granuloma in man. It is pathogenic for guinea-pigs on inoculation into the lungs.

COMMENT

The history and course of the disease indicate that in this instance the port of entrance was the skin on the back. The patient did not remember any trauma, but admitted having scratched and frequently squeezed his acne papules. It can well be conceived that on such an occasion he inoculated the germ with his finger-nails into such a lesion. This may be true of the subsequent granulomas, but as these occurred in places where acne was absent, transmission by way of the blood stream is more likely. The latter theory is supported by the formation of a metastatic process in the brain. The rapidity with which this tumor developed is in favor of an infectious process rather than a new growth. The ultimate proof that this lesion was actinomycotic in origin is lacking, since efforts to obtain permission for an autopsy failed. That the minute

pieces of tissue removed at the site of operation yielded no growth is not surprising as they were taken from an area remote from the suspected lesion. I am not sure that Actinomyces phenotolerans was present in the spinal fluid, as the threads and sporelike bodies failed to grow. The low cell count is against the presence of pathogenic organisms in the spinal canal. Nevertheless, the conclusion appears justified that we were dealing with a primary actinomycosis of the skin with metastatic granulomas in the skin and brain. Auto-inoculation was not carried out, since no further information was expected from such a procedure, and the pathogenicity of the organism recovered on numerous occasions in pure cultures seemed sufficiently established.

Primary actinomycosis of the skin is rare. Rauber,[2] in 1926, collected the reports of 70 cases from the literature. Harbitz,[3] in 1923, studied a series of 133 consecutive cases in Norway and gave the incidence of primary infection of the skin as 3 per cent. Involvement of the central nervous system is likewise rare. According to Bell,[4] up to 1922, only 46 instances were on record in the literature. However, I am inclined to believe that primary actinomycosis of the skin as well as actinomycotic involvement of the central nervous system is more frequent than the reports indicate, as the diagnosis may be very difficult and as there is a great deal of confusion as to the mycology and proper terminology of the condition.

While the world literature terms the clinical condition actinomycosis, the causative organism is known to the English as Nocardia, to the French as Discomyces and to the Germans as Actinomyces. Generic names less frequently used are Bacterium, Streptothrix, Oospora and Cladothrix. All these names are synonyms. The suggestion was made to employ the term Actinomyces for the nonspore-bearing forms of ray fungi, and Nocardia for the spore-bearing forms, but this subdivision has been abandoned. Also the subdivision Discomyces and Cohnistreptothrix is not in general use. In this country the report of the Committee of the Society of American Bacteriologists on Characterization and Classification of Bacteria is regarded as the ultimate authority on bacterial nomenclature, and Actinomyces (Harz, 1877) was accepted as the generic name without any further subdivisions.

It has been proposed also that organisms forming grains in tissue should be termed Actinomyces, and those which do not, Streptothrix.

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2. Rauber, Arnold: Zur Kenntnis der primaeren Aktinomykose der Haut, insbesondere der Genitalgegend, Acta dermat.-venereol. **6**:493, 1926.

3. Harbitz, Francis: Verlesungen der pathologischen Anatomie ueber Syphilis, Lepra und Aktinomykosis, Oslo, Steenske Verlag, 1923; reviewed in Zentralbl. f. Haut. u. Geschlechtskr. **14**:231, 1924.

4. Bell, H. H.: Infection of Meninges and Lungs by Species of Actinomyces, J. Infect. Dis. **30**:99 (Jan.) 1922.

Grubauer [5] reported a case in which the grains were present in an empyema of the appendix but not in the pleural exudate, yet the organism isolated in both were identical. In my own case, diligent search failed to reveal grains in sections and exudate, but grains with radiating club-shaped filaments were found in the lungs of experimentally infected guinea-pigs. Whether granules are formed or not depends not so much on the species of the fungus as on the reaction of the tissue. With one of the best known surface parasites, Achorion Schoenleinii, Tarozzi and Barbanti [6] produced in animals granulomatous lesions containing grains composed of mycelial elements. This clearly demonstrates that the granule formation in a host is a variable factor and therefore cannot be used in the differentiation and classification of fungi. But it forces us to still another conclusion: The definitions of Chalmers and Archibald [7] are open to criticism. These authors designate as actinomycosis "those forms of mycetoma with granules composed of fine, non-segmented mycelial filaments in which usually the wall is not clearly defined from the contents and in which chlamydospores are absent."

This scope is by far too narrow. In keeping with the etiologic classification of disease in other fields of medicine, it seems logical to designate all manifestations caused by species of the genus Actinomyces as actinomycosis. A review of the literature shows that widely differing conditions have been proved as caused or at least accompanied by Actinomycetes. The variety of clinical aspects is paralleled only by the most common pathogenic micro-organsims, the staphylococci and streptococci. In spite of the extensive research on the mycology of the Actinomycetes, our knowledge of these organisms is still rudimentary. Actinomycetes are ubiquitous and therefore common contaminants in cultures; some are saprophytes in the oral cavity and only a few are pathogenic; some of these respond easily to treatment; others resist all efforts. It almost seems that "Actinomyces" was a term as loose and vague as "bacillus." This contention is supported by the fact that biologic reactions are of little, if any, value in the treatment and diagnosis of actinomycosis. Some day we may be able to differentiate Actinomycetes as well as the colon, typhoid or hay bacilli. Until then, it seems advisable to follow with Actinomycetes the same course as with the common pyogenic organisms and retain the clinical and pathologic terminology. As examples of such a terminology may be cited: (1) mycetoma actinomyceticum; (2) pseudomycetoma actinomyceticum; (3)

5. Grubauer, Fred: Zur Diagnose der Strahlenpilze und der Strahlenpilzkrankheit, Virchows Arch. f. path. Anat. **256**:434, 1925.

6. Tarozzi, G., and Barbanti, R.: Actinomycosi e monosporosi, Atti d. r. Accad. di. sc., lett. ed arti, Modena (sez. sc.) s. 3a **12**:321, 1916.

7. Chalmers, A. J., and Archibald, R. G.: A Sudanese Maduromycosis, Ann. Trop. Med. **10**:169 (Sept.) 1916.

actinomycosis of the brain, liver and lungs; (4) conjunctivitis, dacryocystitis, parotitis actinomycetica; (5) elephantiasis actinomycetica; (6) actinomycosis cutis gangraenosa; (7) dermatitis actinomycetica; (8) impetigo actinomycetica; (9) trichomycosis axillaris actinomycetica; (10) lingua nigra actinomycetica, and (11) keratolysis plantaris actinomycetica (Acton and McGuire [8]).

SUMMARY

A case of primary actinomycosis (pseudomycetoma) of the skin with metastases is reported.

The causative agent was a hitherto undescribed species: Actinomyces phenotolerans.

Species of the genus Actinomyces may produce a variety of clinical manifestations as great as those caused by the common pyogenic organisms.

524 Osborn Building.

ABSTRACT OF DISCUSSION

DR. HOWARD FOX, New York: It is rather consoling to hear of cases like this of definitely proved actinomycosis in which the granules were not present. It is known that the characteristic granules may not be present in this disease. On the other hand, it is known that granules may be found in cases which have no relation to actinomycosis. They occur in the tonsils, about the teeth and in botryomycosis, a disease which chiefly affects animals and which is apparently due to a streptococcus. They also occur in actinobacillosis, a disease in which the clinical picture of actinomycosis is present and which is due to the actinobacillus. Dr. Gammel should be congratulated on his excellent presentation.

DR. HOWARD MORROW, San Francisco: A subject as rare as this should not go by without a great deal of discussion, for every bit of information may be of value to the rest of us.

At present my associates and I have a patient, a Mexican, with an eruption on the side of the leg, confined to a small area below the knee. A sinus and abscess have been present for a few months. He is a laborer and on this account we did not wish to sacrifice his knee. Thus we had an opportunity to study the case from etiologic and therapeutic standpoints. The English have long taught that actinomycosis is diagnosed by finding granules, and that without the granules the disease is not actinomycosis, but this paper proves that this theory is not correct. Of course, without microscopic examination one cannot diagnose the diseases with which one comes in contact. The case I mentioned was diagnosed as actinomycosis on account of the finding of yellow granules. However, it was found that the organism was aerobic and not anaerobic, and that took it out of the class of Actinomyces. Because it was aerobic and of a type simulating

8. Acton, H. W., and McGuire, C.: Keratolysis Plantaris Sulcata; Lesion Due to Actinomycotic Fungus, Indian M. Gaz. **65**:61 (Feb.) 1930; Actinomycotic Lesions of Skin of Hands and Feet Due to Actinomyces Keratolyticus n. sp., Indian M. Gaz. **66**:65 (Feb.) 1931.

maduromyces, we classified the organism as Actinomyces madurae. Dr. Karl Meyer stated that the condition in this case should be classed as actinomycosis mexicana.

In regard to the treatment, the surgeons did not desire to operate for the reasons I have mentioned, and so simple incisions were made through the sinus and into the abscess; the abscess was curetted, and the various cavities were packed with a 4 per cent solution of copper sulphate. The pain was so severe that it necessitated giving the patient morphine. After the pain subsided, the cavities were packed with gauze saturated with chaulmoogra oil, and the result was so good that we thought he would be cured, but now he has had a recurrence. We feel that the good results were obtained from the copper sulphate and not the chaulmoogra oil. He was also given chaulmoogra oil by mouth, as well as the packs.

Dr. William H. Guy, Pittsburgh: I was unable to gather from Dr. Gammel's necessarily brief description all the points concerning the organism, and I do not know whether or not it was similar to the one from the case recorded as nocardiosis cutis gangraenosa. The clinical findings in Dr. Gammel's case were very different from those in mine, in which the patient's condition cleared up under blood transfusions and intravenous administrations of colloidal iodine. I, perhaps erroneously, assume that the author considers the organisms isolated from the two cases identical or closely related in view of the reference to nocardiosis in his opening paragraph. Submission of cultures to bacteriologists and mycologists often leads to as many different classifications as there are experts expressing opinions. I feel that too much is included under the name actinomycosis. Actinomycosis of the skin is a definite clinical picture in which the ray fungus is found. With materially different clinical pictures, and organisms belonging to the family Actinomycetaceae, but different from the ray fungus, I feel that the conditions should not be called actinomycosis. For such cases the nomenclature should be in keeping with the subgroup classification of the organism.

Dr. John A. Gammel, Cleveland: The fact that actinomycotic granules may be absent has been mentioned in the literature for a long time, but physicians do not always keep this in mind. The more I learn about the subject the more I am convinced that the finding of granules is not of great importance. A few months ago Dr. Moritz and I published a paper on "Experimental Monosporosis." The organism, Monosporium apiospermum, has been found as cause of madura foot a number of times. When a suspension of spores was injected into the knee joints of rabbits lesions with mycotic granules developed in some animals, and in others there were no granules. Actinomyces asteroides was injected into control animals. The histologic picture was identical; monosporosis could be differentiated from actinomycosis only by the appearance of the organism in the tissue.

Referring to Dr. Guy's remarks, I must confess that I do not consider myself enough authority to decide if his organism and ours are identical or not. I left the question of identification up to Dr. Werkman, who has done splendid work along this line. I feel that the genus Actinomyces will have to be subdivided, but to do this is up to the Committee of the Society of American Bacteriologists on Characterization and Classification of Bacteria.

IODOBISMITOL: CLINICAL EXCRETION OF BISMUTH

P. J. HANZLIK, M.D.

H. G. MEHRTENS, M.D.

AND

J. B. SPAULDING, A.M.

SAN FRANCISCO

This paper presents the final results on the urinary and fecal excretion of bismuth after the administration of iodobismitol in man and in animals. Since the publication of a preliminary report,[1] the number of subjects for this study has been increased, the total number of human beings being twenty-two, and the number of rabbits, thirteen. For one reason or another, not all human beings and animals permitted the study of complete excretion. Satisfactorily completed excretions were obtained with ten persons and seven rabbits.

METHODS

The iodobismitol was injected intramuscularly in both patients and rabbits. The iodobismitol contained 6 per cent sodium iodobismuthite (containing 21.5 per cent bismuth) and 12 per cent sodium iodide in ethylene glycol (description in "New and Nonofficial Remedies"). The doses used were of therapeutic order, ranging from a single dose of 0.033 cc. per kilogram (2 cc. for an adult weighing 60 Kg.) to multiple doses. The total number of doses in the completed experiments was 20, spaced as indicated in chart 1, and in the incomplete experiments, the total was sixty. Patients of both sexes were used. They were confined in bed and ate freely of the hospital diet without control of fluid intake. Urine was collected daily, and feces were obtained at least three times weekly, and in some cases daily, until the daily excretion of bismuth in the urine reached about 0.2 mg., when the collections were stopped. The excretion of bismuth might be more rapid and com-

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From the Department of Pharmacology and the Neuropsychiatric Division of the Department of Medicine, Stanford University School of Medicine.

The clinical part of this work was due largely to the encouragement of Dr. Henry George Mehrtens, whose premature death on Feb. 28, 1933, deprived us of an inspiring and loyal colleague.

1. Hanzlik, P. J.; Mehrtens, H. G.; Gurchot, C., and Johnson, C. C.: Iodobismitol: Soluble Bismuth Product for Use in Treatment of Syphilis: Preliminary Report, J. A. M. A. **98**:537 (Feb. 13) 1932.

plete in ambulatory patients than in those at rest in bed, but the former are not satisfactory for quantitative studies. The rabbits were full-grown adults, kept in individual cages designed for separate collection of feces and urine.

The analytic procedures used were the same as those previously described [2] and need not be described again. The analysis of feces presented greater difficulties than that of urine. Preliminary inciner-

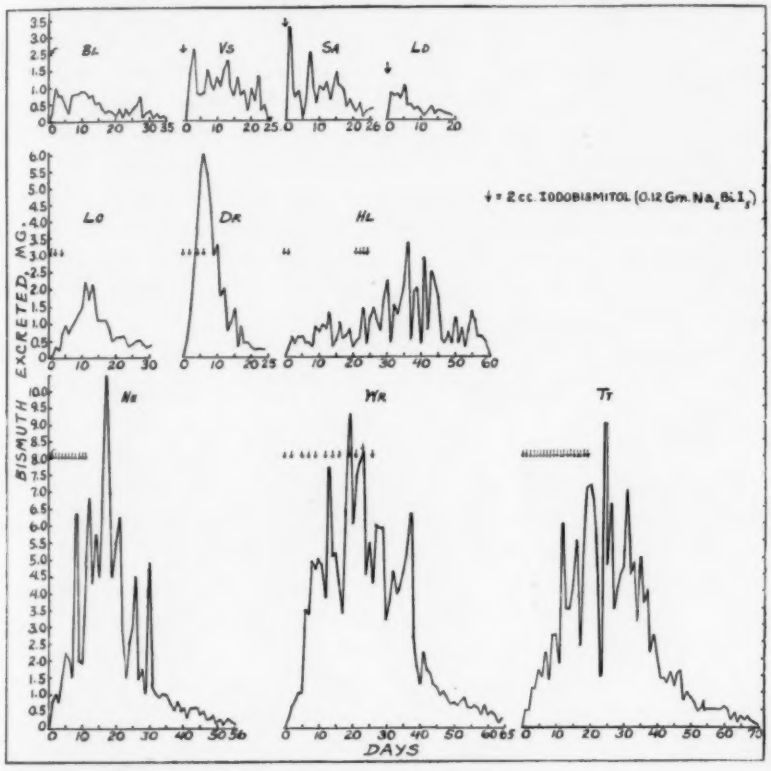

Chart 1.—Daily urinary excretion of bismuth after different doses of iodobismitol in patients.

ation in an electrical furnace was tried, as was done with tissues,[3] but the recovery of bismuth was not as good as with wet oxidation, which was used with both urine and feces throughout.

2. Hanzlik, P. J., and Mehrtens, H. G.: Clinical Excretion of Bismuth: Bismuth Metal, Arch. Dermat. & Syph. **22**:483 (Sept.) 1930.

3. Hanzlik and Spaulding: J. Pharmacol. & Exper. Therap. **49**:257, 1933.

Urinary Excretion of Bismuth After Therapeutic Doses of Iodobismitol

Patient	Diagnosis	Total Iodobismitol Administered: Sodium Iodobismuthite, Gm.	Total Iodobismitol Administered: Number of Doses	Total Percentage of Bismuth Excreted‡	Peak of Excretion, Days
Complete					
Bl ♀	Hysteria	0.12	1	51 (34)	3
Vs ♂	Cerebrospinal syphilis	0.10	1	87 (25)	2
Sa ♂	Parkinson's disease	0.10	1	76 (26)	1
Ld ♂	Epilepsy	0.12	1	30 (20)	6
Lo ♀	Cerebrospinal syphilis; tabes	0.33	3	35 (31)	12
Dr ♂	Cerebrospinal syphilis	0.48	4	43 (24)	6
Hl ♀	Retrobulbar neuritis	0.72	6	35 (59)	36
Ne ♂	Dementia paralytica	1.44	12	38 (56)	18
Wr ♀	Hysteria	1.44	12	63 (64)	19
Tt ♂	Dementia paralytica	2.40	20	34 (69)	25
Incomplete					
Nn ♀	Parkinson's disease	0.12	1	11 (8)	2
Mn ♂	Angioneuritis	0.20	1	12 (10)	3
Sc ♂	Cerebrospinal syphilis; tabes	0.24	1	8 (6)	3
Gn ♂	Cerebrospinal syphilis; bulbar palsy; prostatitis	0.48	3	14 (14)	3
Mk ♂	Cerebrospinal syphilis; dementia paralytica	0.30	3	28 (14)	9
Me ♂	Cerebrospinal syphilis; tabes	0.80	4	8 (12)	6
Ca ♂	Bulbar palsy	1.80	9	13 (18)	112 (?)
Dt ♀	Cerebrospinal syphilis	1.08	9	27 (22)	13
Hn ♂	Cerebrospinal syphilis	2.04	17	6 (16)	16
Yk ♀	Cerebrospinal syphilis	2.28	19	8 (20)	22 (?)
Kn ♂		....	57	20 (55)	14
Ws ♂	Cerebrospinal syphilis; dementia paralytica	7.20	60	15 (26)	21
Rabbits Number		Mg. per Kg.			
11		43.0†	1	44 (22)	1
94		1.8	1	37 (33)	6
95		3.6	2	46 (45)	6
93		3.6	2	62 (36)	5
101		5.4	3	44 (37)	13
97		21.6	12	47 (66)	22
98		21.6	12	48 (30)	10
Rabbits Number		Mg. per Kg.			
10		400.0#	1	15 (25)	6
3		150.0#	1	24 (22)	6
28		126.0#	1	23 (33)	2
96		3.6	2	21 (45)	8
100		5.4	3	22 (10)	10 (?)
99		5.4	3	17 (21)	18

Comment
Incomplete collection
Died
Urine spilled
Urine spilled
Died
Urine not voided

† Intravenous injection. ‡ The figures in parentheses indicate the duration of excretion in days. # Extratherapeutic doses.

URINARY EXCRETION IN HUMAN SUBJECTS

Single Doses.—The daily excretion after different doses in human subjects can be seen from the curves in chart 1, and the total excretion is presented in the table.

Single 2 cc. doses of iodobismitol (0.12 Gm. of sodium iodobismuthite) resulted in a variable excretion in the four patients (Bl, Vs, Sa and Ld) used. The fluctuations were more marked in Vs and Sa than in Bl and Ld, the variations being correlated with corresponding fluctuations in the output of urine. The maximum daily quantities of bismuth excreted varied from 1 to 3.3 mg. The peak of excretion was reached in from one to six days (median, two and one-half days). The excretion then gradually decreased to from 0.1 to 0.2 mg. at the end of from twenty to thirty-five days (median, twenty-six days). After this, bismuth continued to be excreted, but the minute amounts could not be accurately estimated. Therefore, the exact duration of excretion of bismuth is not known, but it certainly exceeds one month after the injection of the iodobismitol. The total bismuth recovered from the urine during the periods of the experiments ranged from 30 to 87 per cent of the total amount administered (median, about 63 per cent). The very small fecal excretion (Bl and Ld) suggests that the bismuth unaccounted for, or from about 23 to 70 per cent (median, 37 per cent), probably escaped with the urine over a period of weeks in quantities too small to estimate by the analytic method used.

Multiple Doses.—The excretion after the equivalent of about one week's medication, or a total of three or four doses given on alternate days, can be seen in the curves for Lo and Dr. The daily maximum excretion by Dr, who received one more dose of iodobismitol, was 6 mg. The peaks occurred on the twelfth (Lo) and the sixth (Dr) day. The duration of excretion was thirty days (Lo) and twenty-five days (Dr), with smaller fluctuations than after the single doses. Despite the higher dosage given these subjects, the excretion did not last longer, probably because the daily excretion around the peak level was three or four times greater, like the number of doses. The total urinary excretion of these patients was 35 and 43 per cent of the total bismuth administered, which compared with the total excretion of Bl and Ld and with the median excretion of all subjects given single doses.

Patient Hl (chart 1) received six doses of iodobismitol (equal to a total of 0.72 Gm. of sodium iodobismuthite) in a little over three weeks. The day-to-day fluctuations in the excretion were considerable. The peak occurred on the thirty-sixth day after the first dose and the twelfth day after the last dose, the maximum daily excretion being 3.3 mg. The total urinary excretion was 35 per cent two months after the first injection. The excretion lasted thirty-six days after the last injection.

Although the fecal excretion in this patient was not determined, the remainder, or 62 per cent, of the bismuth probably continued to be excreted slowly in minute amounts in the urine for weeks.

Ne and Wr received twelve doses each, and Tt, twenty doses, of iodobismitol (equal to 1.44 Gm. and 2.4 Gm. respectively of sodium iodobismuthite) within less than one month. Again the day-to-day fluctuations were considerable and paralleled the output of urine. Peaks in the excretion were reached in from eighteen to twenty-five days (median, nineteen days) after the first injection of iodobismitol. The maximum daily amounts of bismuth excreted ranged from 9 to 10.5 mg. The excretion lasted from fifty-six to sixty-nine days (median, sixty-four days). The total excretion in the urine was found to vary from 34 to 63 per cent (median, 38 per cent). The fecal excretion, according to determinations on Wr and Tt, accounted for only about 10 per cent more bismuth, and therefore the remainder of the injected bismuth continued to be excreted in the urine, as in all previous cases. It is interesting to note that the duration of excretion was no longer than after medication for from one to three weeks in Lo, Dr and Hl, but of course the daily elimination during the early periods of excretion was enormously increased; that is, the rate of removal was greater as the dose increased. Apparently rather high concentrations of bismuth can pass through the kidney without impairment of its excretory function for either bismuth or water. The usual clinical examinations for albumin and casts revealed nothing abnormal.

Incomplete Excretions.—The results for twelve patients with incomplete urinary collections have been included in the table. The collections were generally fair up to the peak of bismuth excretion. Certain tendencies in these results agreed with characteristics of the excretion in patients with complete collections. For instance, not more than one fifth of the total bismuth after single doses of iodobismitol, and about one-half after multiple doses, was excreted before the elimination reached a daily maximum. This suggests that from one half to four fifths of the bismuth is excreted in a slowly declining curve when practical difficulties of controlling patients for sufficiently long periods arise. The time for the peaks of excretion agreed closely with those of complete excretions: after single doses of iodobismitol, three days; after four doses, six days; after six doses, nine and twelve days, and after nineteen and twenty doses, twenty-two and twenty-five days. Further than this, the incomplete results need no discussion.

Relationship of Dosage of Iodobismitol to Duration of Urinary Excretion.—The duration of bismuth excretion in days (table) has been mentioned in the preceding sections. A recapitulation at this point of the possible significance of the duration for medication with

iodobismitol may be of interest. Chart 2 indicates graphically the correlation between the number of doses of iodobismitol and the number of weeks of bismuth excretion. The duration of bismuth excretion reflects the sojourn of bismuth in the body. It is seen that bismuth remains in the body for over three weeks (twenty-six days) after a single injection of iodobismitol and that the duration is not longer (twenty-four days) after three alternating injections given in one week. With a course of six injections within twenty-five days (nearly four weeks) bismuth tends to be retained for at least five weeks. The same holds practically for a one month course of medication with twelve alternating doses. Twenty successive daily injections, or intensive medication for nearly three weeks, medicate the body for about four weeks longer than the injection period, or for about seven weeks. While the data are too limited to indicate desirable courses of antisyphilitic medication with

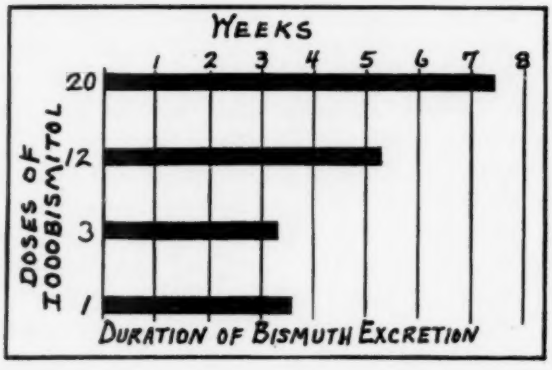

Chart 2.—Clinical duration of bismuth excretion (sojourn in body) according to dosage of iodobismitol.

iodobismitol, the possibilities for such periods of medication, in order to obtain a well sustained action of bismuth, are conveniently indicated by the graphic correlation in chart 2. This clearly indicates that the elimination of bismuth is not too rapid, although it begins promptly after injection of iodobismitol. Hence, as frequent injections should not be necessary as with some other soluble products; this achieves comparative economy in medication and freedom from unnecessary side-actions and poisoning.

URINARY EXCRETION IN RABBITS

For added interest and completeness of the work, the excretion of bismuth was studied in thirteen rabbits (seven complete and six incomplete excretions [table]). The iodobismitol was injected intramuscularly in single and multiple doses, the latter being spaced in three and twelve divided doses as in the case of patients. The fecal excretion was studied

in five rabbits and will be referred to later. As for the urinary excretion, the chief items of interest are the total excretion, the peak and the duration. The daily excretion was extremely variable, owing partly to the great variation in urination of rabbits; frequently animals would not void for a whole day and sometimes not for two or three days. Water, cereals and cabbage were consumed freely, and the fluid intake was not controlled. No specimens of urine were lost while the rabbits were in cages, so that in all cases collections were complete except for the accidents indicated in the table.

It is seen that the total percentage of excretion was of the same order of magnitude regardless of the number of doses of iodobismitol injected. The total proportion of bismuth excreted in the urine after twelve doses (rabbits 97 and 98) was not much greater (47 and 48 per cent) than after two doses (46 and 62 per cent). After three doses, 44 per cent was excreted (rabbit 101), and after one dose, 44 and 37 per cent (rabbits 11 and 94). The close agreement between the results in different rabbits indicates a median value of 44 per cent for the total excretion. The remainder of the bismuth could not be accounted for by the fecal excretion, which amounted to not more than 13 per cent (median, 4 per cent). Hence, again, about one-half the bismuth administered continued to be eliminated in minute quantities in the urine, probably for weeks. The peak of excretion after single doses tended to be delayed (complete and incomplete excretions) as compared with that for human subjects, but after multiple doses, i. e., from two to twelve doses, the peaks were comparable though not identical. The duration of excretion (complete experiments) was similar to that in patients, i. e., from three to four weeks, and probably was not more variable. On the whole, the urinary excretion of bismuth in rabbits receiving iodobismitol was comparable in all essential respects with that in human subjects. While human subjects are better suited and more valuable for excretion experiments of this kind than are rabbits, the latter may be used alternatively in case clinical material is not available.

EXCRETION IN FECES

Human Subjects.—Patients Bl, Ld, Lo, Dr, Wr, Tt and Dt excreted 7.5, 3, 4, 2, 3.3, 8 and 2 per cent, respectively, of the total bismuth which they received (as iodobismitol); the median total excretion of all patients was 3.3 per cent. The peak of fecal excretion coincided with that of urinary excretion in patients Ld, Tt and Dt, but in Dr it occurred seven days later, in Lo ten days later and in Bl fourteen days later. The total fecal excretion was not influenced by the total dosage of iodobismitol, which ranged from one to twelve doses (0.12 to 1.44 Gm.) in these patients. These results are based on analyses of not less than three weekly specimens, representing twenty-four hour collections, and in a few cases daily specimens.

Rabbits.—Rabbits 93, 94, 95, 96, 97, 98, 99, 100 and 101 excreted 13, 11, 4, 2.5, 2, 1.1, 6.7, 2 and 6 per cent, respectively, of the total bismuth administered (as iodobismitol); the median total excretion of all animals was 4 per cent. Again, the percentage of fecal excretion was not affected by the dosage, and it was comparable in amount and variability with that of patients. These results were obtained by analysis of daily specimens of feces from these rabbits.

Although studies of fecal excretion are never as satisfactory as those of urinary excretion, the results with iodobismitol in animals and in man indicate that only a very small and practically negligible portion of the injected bismuth escapes with the feces. This is true of therapeutic doses of bismuth products in general.

COMPARISON WITH OTHER BISMUTH PRODUCTS

The clinical excretory results with iodobismitol in therapeutic doses compare favorably with those for other soluble bismuth products, such as sodium bismuth tartrate and sodium potassium bismuth tartrate in aqueous or lipoid mediums.[4] The median total excretion of bismuth after these sodium bismuth tartrates is about 45 per cent, and after iodobismitol, 40 per cent, regardless of dosage. The excretion in animals given injections of bismuth products in doses of therapeutic order is also comparable, but owing to the differences in the species of animals used by different investigators, exact comparison is not possible. The peaks of excretion and the maximum daily excretion of bismuth are similar to those for sodium bismuth tartrate. There is no doubt that urinary excretion of bismuth after iodobismitol is more definite, regular and complete than after the various insoluble products used in lipoid or aqueous mediums.[4] On the whole, the excretory results with iodobismitol correlate with the results of roentgen examination of muscles into which injections have been made in patients [5] and with the results of studies of muscular absorption in animals.[3] They show that the bismuth of iodobismitol is promptly absorbed and distributed in the body. Its removal, however, appears to be somewhat slower than with sodium bismuth tartrate, a tendency which is in its favor as an antisyphilitic agent.

CONCLUSIONS

1. The excretion of bismuth in urine and feces was studied in patients and animals receiving intramuscular injections of iodobismitol in doses of therapeutic order.

4. Hanzlik, P. J., and Mehrtens, H. G.: Comparative Excretion and Absorption of Different Bismuth Products: Summary Report, Arch. Dermat. & Syph. **22**:861 (Nov.) 1930.

5. Hanzlik, P. J.; Seidenfeld, M. A., and Johnson, C. C.: Local, Irritant and Toxic Action of Sodium Iodobismuthite and Iodobismitol, J. Pharmacol. & Exper. Therap. **46**:1, 1932.

2. The excretion was similar qualitatively and quantitatively in man and in animals, and was characterized by promptness of onset, considerable daily irregularity, long duration and incompleteness.

3. The daily clinical excretion of bismuth in urine varied directly with the dosage, the maximum being generally reached after single doses on the third day, after three doses, or one week's medication, on about the sixth day, and after from twelve to twenty doses, or one month's medication, on about the twentieth day, after the beginning of administration.

4. The probable sojourn of bismuth in the body after different types of clinical medication with iodobismitol was estimated from the duration of excretion to be about as follows: for a single dose of 2 cc., over three weeks; for three alternating doses in one week, over three weeks; for six or twelve doses within one month, over five weeks, and for twenty daily doses within three weeks, about seven weeks.

5. The total urinary excretion of bismuth in patients ranged from 30 to 87 per cent (median, 40 per cent), and the total fecal excretion ranged from 2 to 8 per cent (median, 3.3 per cent), regardless of dosage. In rabbits, the total urinary excretion ranged from 37 to 62 per cent (median, 44 per cent), and the total fecal excretion ranged from 1.1 to 13 per cent (median, 4 per cent), regardless of dosage. The remainder, or roughly one-half the administered bismuth, continued to be excreted in traces in the urine for long periods, probably weeks.

6. The clinical excretion of bismuth in the urine, as well as the excretion by experimental animals, after therapeutic doses of iodobismitol compares favorably with the excretion of other soluble bismuth products; the fecal excretion is slight and practically negligible. The results of the study of the excretion of bismuth after iodobismitol correlate closely with the previously reported results of studies of absorption by roentgen examination of muscles in patients and by analysis of muscles in animals.[6]

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6. After this paper was in type, confirmation of all our results with iodobismitol came to our attention. Strandberg and Sjögren (Acta dermat.-venereol. **14**:1, 1933) confirmed the anionic character, absorption, excretion, cerebrospinal fluid penetration and clinical antisyphilitic potency of iodobismuthite; Levaditi, Vaisman, Manin and Schoen (Bull. Soc. franç. de dermat. et syph. **40**:738 [May] 1933) confirmed the comparatively low toxicity of iodobismitol, its antisyphilitic potency in experimental syphilis and its cerebrospinal penetration in monkeys, and da Nova Gomes and de Oleveira of São Paulo, Brazil, in a personal communication, and Carrillo, Schujman and Campos (Semana méd. **2**:1710 [Nov. 30] 1933) confirmed the clinical antisyphilitic potency and cerebrospinal fluid penetration of this drug.

News and Comment

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY EXAMINATIONS FOR CERTIFICATES

The American Board of Dermatology and Syphilology will hold written examinations for candidates for a certificate on April 30, 1934, in the following cities: New York, St. Louis, Boston, Cleveland, San Francisco, Philadelphia and Chicago. If a sufficient number of applicants register for the examination from other districts, additional examinations will be held in other cities. This examination will be for applicants in both Group A and Group B. The oral examination for both Group A and Group B will be held in Cleveland on June 11 and 12, at the time of the American Medical Association meeting.

All applicants for a certificate who intend to take these examinations in either group must send their applications and other credentials to the office of the secretary before March 14, 1934. Application blanks and further information may be obtained from the secretary, Dr. C. Guy Lane, 416 Marlboro Street, Boston, Mass.

FIFTH CONGRESS OF DERMATOLOGISTS AND SYPHILOGRAPHERS SPEAKING THE FRENCH LANGUAGE

The Fifth Congress of Dermatologists and Syphilographers Speaking the French Language will take place at the Faculty of Medicine of Lyon on July 19 to 21, 1934, and will be presided over by Professor Nicolas (Lyon). The following subjects will be reported: (1) Etiology and Treatment of Erythematous Lupus, (2) Diagnosis of Chancroidal Bubo and (3) Cutaneous Accidents in Antisyphilitic Treatment. Communications on other subjects will not be accepted.

The dues will be 150 francs, reduced to 100 francs for members of the Association of Dermatologists and Syphilographers Speaking the French Language. The dues for associate members (wives, children, students) is 50 francs. They should be sent to the following address: Lyon C/c 83-88, 5e Congrès des Dermatologistes et Syphilographistes de Langue Française, 24 Rue Ste-Hélène, Lyon (2e).

Further information may be secured from Jean Lacassagne, Secrétaire adjoint, 26 Rue de la République, Lyon, or M. Carle, Secrétaire général, 11 Rue Emile-Zola, Lyon.

Abstracts from Current Literature

SPIROCHAETAL FINDINGS IN THE BRAINS OF PARETICS TREATED WITH MALARIA. NICHOLAS KOPELOFF and NATHAN BLACKMAN, Am. J. Psychiat. **13**:21, 1933.

The authors examined the brains of thirty-nine patients with dementia paralytica who had been treated with malaria and the brains of ten patients with dementia paralytica who had not been treated with malaria. The average number of malarial paroxysms was nine per patient. Many of the patients showed clinical improvement immediately after the injections but later became worse. Spirochetes most of which were degenerate were found in six of the thirty-nine brains which had been treated, and normal spirochetes in eight of the ten brains which had not been treated. From the results the authors believe that malaria artificially induced may destroy the spirochetes in the brains of persons with dementia paralytica, or may alter the morphology of Spirochaeta pallida to make it degenerate in appearance. The longer the interval of time between the inoculation and the death of the patient, the more typical is the spirochete found in the brain.

PERLSTEIN, Chicago.

A TAPE TEST WITH TUBERCULIN OINTMENT. ERNEST WOLFF and MAX H. TEITLER, Am. Rev. Tuberc. **27**:308 (March) 1933.

An ointment was prepared containing a highly concentrated tuberculin and killed tubercle bacilli in a base able to penetrate the cutis. The test was made in the paravertebral region between the eighth and eleventh thoracic vertebra. After cleansing, a drop of the ointment was applied to the skin and covered tightly with a 2 inch (5 cm.) square of adhesive tape. An identical ointment base without tuberculin was applied to the opposite side as a control. The test was read within forty-eight hours. The reaction may be clearly observed ten minutes after the removal of the adhesive tape. A positive reaction is indicated by papules, erythema, induration and yellow pigmentation. The color varies from pale pink to vivid red, according to the intensity of the reaction. The peak of the reaction is reached after seventy-two hours. Medium reactions show definite scaling up to approximately ten days. In nearly every positive case there was some itching over the test area, but systemic reactions did not occur. The agreement between the test with the ointment and the intracutaneous test in all dilutions, as applied to 190 children, was 95.8 per cent. This test is generally comparable in result with the intracutaneous test with old tuberculin in a dilution of 1:100.

EUGENE SMITH, Ogden, Utah. [AM. J. DIS. CHILD.]

RODENT ULCER OCCURRING IN MAN AND WIFE. STUART GORDON, Canad. M. A. J. **29**:181 (Aug.) 1933.

The husband, aged 37, had a lesion on the lower eyelid for six years. The wife, aged 32, had a lesion on the upper lip of recent origin. The author considers three possibilities: (1) coincidence, (2) direct grafting of the tumor and (3) implantation of a virus. Against the first is the fact that both are relatively young. Against the second is the fact that no history of any injury to the involved area could be obtained. No comment is made as to the third possibility.

PSORIASIS AND GOLD SALTS. ALBERIC MARIN and F. L. BOULAIS, Canad. M. A. J. **29**:189 (Aug.) 1933.

The authors' experience with sixteen cases is that gold has a very limited effect on the course of psoriasis. The drug was administered intravenously. In one case only the eruption disappeared entirely; in all the others, lesions were present after five months. The incidence of reactions was high.

H. RATTNER, Chicago.

PELLAGRA IN A CHILD TWO YEARS OLD. EUGENE T. MCENERY, J. Pediat. **2**:478 (April) 1933.

A fatal case of pellagra occurring in a Mexican boy, aged 2 years, is reported. No fresh fruits, vegetables or meat had been given. Improvement under treatment was progressing slowly except for two severe reactions following exposure to ultraviolet rays, when the child died suddenly.

ACRODYNIA. FRITZ MEYER and ELLWOOD C. WEISE, J. Pediat. **2**:750 (June) 1933.

A case of acrodynia in a 4 year old boy is reported. The blood and urine contained appreciable amounts of arsenic. Recovery followed the repeated administration of sodium thiosulphate. This case furnishes additional evidence that arsenic is an etiologic factor in acrodynia.

ACRODYNIA. KENNETH D. BLACKFAN and CHARLES F. MCKHANN, J. Pediat. **3**:45 (July) 1933.

The forty-four cases of acrodynia seen at the Harvard Clinic during the past nine years are discussed from the standpoint of symptoms, physical findings, laboratory data and postmortem observations. The authors favor the view that the manifestations of acrodynia are dependent on a diffuse disorder of the central nervous system with overstimulation of both the sympathetic and parasympathetic divisions.

SERUM PROTEINS AND LIPOIDS IN THE ECZEMA OF INFANTS AND CHILDREN. HAROLD K. FABER and DOROTHY B. ROBERTS, J. Pediat. **3**:78 (July) 1933.

The serum protein of infants with eczema was found frequently to show deviations from the normal. A high content of albumin, a low content of globulin and a high albumin-globulin ratio occurred more frequently in patients with eczema than in normal children. In half the patients with eczema the level of the serum cholesterol was more than 200 mg. per hundred cubic centimeters, but in a few instances the cholesterol content was very low. The results indicate that in eczema there is often instability in the protein and cholesterol metabolism, which is probably to be regarded as a secondary or subsidiary manifestation of the general disturbance. No difference in the phospholipids of the serum was detected in the patients with eczema as compared with the controls.

LEMASTER, Evanston, Ill. [AM. J. DIS. CHILD.]

AETIOLOGY AND TREATMENT OF PINK DISEASE. J. VERNON BRAITHWAITE, Arch. Dis. Childhood **8**:1 (Feb.) 1933.

Rather convincing evidence is given that pink disease may be due to abnormal reactions to daylight in an infected child. A high percentage of cases occur in the summer months. The blood calcium is usually raised. Intravenous or intraperitoneal injections of sodium citrate caused a temporary improvement. Various methods of treatment were used, including vitamin B and raw liver, ultraviolet radiation, vitamins A and D and confinement in a red window glass room. Patients with pink disease tend to recover in a hospital. The author believes that this is due to the fact that the patients are kept indoors and protected from the sun's rays. Ultraviolet radiation did not have much effect on the course of the disease. The harmful short wave rays in sunlight are not given off by the mercury vapor or the carbon arc lamp. Children kept in a ruby glass room made more rapid recovery than those given other forms of treatment.

KELLY, Milwaukee. [AM. J. DIS. CHILD.]

LICHEN URTICATUS OR URTICARIA PAPULOSA. GEORGE W. BRAY, Brit. J. Child. Dis. **30**:180 (July-Sept.) 1933.

The author briefly reviews the history, symptomatology, differential diagnosis and pathology of lichen urticatus, and discusses the theories regarding the etiology. From his observations he believes that there are two factors involved in the etiology: a dietary factor and a thermal factor. The main dietary agents are products from pigs, such as pork, ham, bacon and lard, and cod liver oil or food containing them. In a small number of cases fish, eggs, potatoes, oats and chocolate may act as additional agents. He believes that oleic acid is the main cause of infection; it occurs in all of these foods. Various fruits may seem to produce attacks, but only in the presence of the fats mentioned. At such times, the fruits may act to aid the absorption of the fat. The thermal factor is evidenced by the frequency of occurrence of lesions in warm weather, after baths and as a sequel to any feverish ailment. Bray's treatment consists in removing the offending fat from the diet and preventing the child from becoming overheated. Mild local medication is used, and internal medication consisting of pepsin and hydrochloric acid.

PERLSTEIN, Chicago.

A SUBSTITUTE FOR THE WASSERMANN TEST FOR UP-COUNTRY WORK, WITH OBSERVATIONS ON 3-AMINO-4-HYDROXYPHENYL DICHLORARSINE HYDROCHLORIDE IN YAWS. K. W. TODD, J. Trop. Med. **36**:233 (Aug. 15) 1933.

The test referred to is the Meinicke turbidity reaction, and the details of the test are given in the article. It was found to be of value in both yaws and syphilis, and the value was not altered by the presence of leprosy. The treatment of yaws with 3-amino-4-hydroxyphenyl dichlorarsine hydrochloride was found to cause a change in the serologic reaction.

JAMIESON, Detroit.

THE IMPORTANCE OF EARLY TREATMENT OF VASCULAR NEVI. E. H. MOLESWORTH, M. J. Australia **2**:217 (Aug. 12) 1933.

It is important to treat a vascular nevus early because usually the nevus increases in size, and the epithelium covering the growth gradually becomes thin by stretching, remaining papery and atrophic in appearance. Hemangiomas are highly sensitive to radiation while they are actively growing, but when growth cases this sensitiveness is greatly diminished. The treatment of choice is irradiation. The author was prompted to write the article because a great many of his patients neglected to seek treatment early on the advice of their physicians.

CHRONIC PARONYCHIA DUE TO MONILIA. IVAN CONNOR, M. J. Australia **2**:312 (Sept. 2) 1933.

Pathogenic monilias were isolated from thirteen cases of chronic paronychia and identified as Monilia albicans. With one exception all the cases occurred in women. The cultures were examined morphologically and biochemically, and their pathogenicity for rabbits was tested. The technic is described in detail.

TRAUMA AND EPITHELIOMA. H. M. MORAN, M. J. Australia **2**:547 (Oct. 21) 1933.

The task of defining the part, if any, played by a single trauma in the causation of cancer cannot at present be satisfactorily fulfilled, since the central problem remains unsolved. The subject is of medicolegal importance, and the author, from a study of the literature and of his own cases, concludes as follows:

1. There is no experimental evidence that an epithelioma can be produced at will in a healthy subject by a single trauma.

2. A single injury is capable of being a determining factor in the causation of epithelioma when applied to a precancerous lesion.

3. An injury to an epithelioma may increase the rate of its growth and the rapidity of its generalization.

4. Violence to a part in a subject suffering from a generalizing epithelioma may determine a local metastasis.

5. Although the factor of coincidence is of importance, one is not justified, in the present state of knowledge, in denying the likelihood of a causal relationship between trauma and epithelioma provided that in the circumstantial evidence brought forward certain postulates are satisfied, namely: (*a*) The previous integrity of the injured part should be established. (*b*) The new growth should appear at the exact site of the injury. (*c*) There should be histologic confirmation of the diagnosis. (*d*) The trauma should be "real and sufficient." There is a wide range of opinion on this postulate and on the length of time which must have elapsed between the alleged injury and the appearance of the growth.

H. RATTNER, Chicago.

EXPERIMENTAL PROOF OF THE TUBERCULOUS NATURE OF ERYTHEMA NODOSUM. R. C. AGUIRRE, Arch. de méd. d. enf. **36**:523 (Sept.) 1933.

In a previous contribution the author reported his findings in a series of sixty cases of erythema nodosum of tuberculous nature. Clinical and roentgenologic examination and tuberculin tests on these patients (children) convinced him that erythema nodosum is in every instance a manifestation of tuberculosis. Bacteriologic proof, however, was lacking in this study, and serious objection has been made by Tachau and others to his rather sweeping assertion.

In the present investigation, Aguirre has been able to provoke generalized tuberculous infection in guinea-pigs by inoculating material from a nodule excised from the left tibial region of a girl 3 years of age.

AMESSE, Denver. [AM. J. DIS. CHILD.]

CHOLESTEREMIA IN PELLAGRA. L. BAILLIF and I. ORENSTEIN, Compt. rend. Soc. de biol. **109**:234 (Jan. 29) 1932.

Of twenty-two persons (four females and eighteen males) exhibiting true characteristics of pellagra, the majority (57 per cent) had blood cholesterol of between 100 and 131 mg. per hundred cubic centimeters. In all the others, except in one female patient who had a cholesterol content of 193 mg., the content was normal. No albumin was found in the urine, and there was no retention of chlorides or nitrogen. The authors venture the conclusion that hypocholesteremia is the general finding in pellagra.

WAHL, Cleveland. [AM. J. DIS. CHILD.]

RARE CASES OF OCULAR SYPHILIS. E. PUSCARIU, Ann. di ottal. e clin. ocul. **60**:901 (Dec.) 1932.

Four cases of primary lesion involving the lids or conjunctiva are reported. Treponemes were demonstrated in three of these cases; in the other no examination was made. The lower conjunctival fornix was involved twice, the upper fornix once, and the border of the lid once. Two patients were infants under 3 years of age; the others were aged 18 and 49 years.

As an unusual secondary manifestation in cases of syphilis, the author reports papules on the bulbar conjunctiva, papules at the limbus with ulceration involving the cornea, ulcerating papular syphilid involving the upper lid and tarsitis. In the last case the lower lid was thickened, with ulceration on the conjunctival surface and a large swelling over the lacrimal sac. The lesions disappeared after five injections of bismuth. Another case of tarsitis was in the tertiary stage and was considered gummatous tarsitis. Another tertiary case showed disseminated choroiditis, gummas of the bulbar conjunctiva and interstitial keratitis (acquired syphilis).

Three cases of destructive ulcerations occurring in late syphilis in which large portions of the lids were destroyed are reported. Two were in hereditary and one in acquired syphilis. The lesions healed quite rapidly with syphilitic treatment, although in all cases much permanent destruction had already occurred.

An unusual late manifestation was a pseudotumor of the orbit. The cornea had sloughed from exposure when the patient was first seen, so the globe, with much of the orbital contents, was eviscerated. Sections showed inflammatory tissue, and the Wassermann test was positive.

S. R. GIFFORD. [ARCH. OPHTH.]

TREATMENT OF FURUNCULOSIS AND MULTIPLE ABSCESSES IN THE NURSLING BY IMMUNOHEMOTHERAPY. MAMERTO ACUNA and FELIPE DE FILIPPI, Arch. argent. de pediat. **3**:721 (Nov.) 1932.

The treatment consisted in preparing an autogenous vaccine from a furuncle or abscess of the affected infant. The vaccine was then injected into one of the parents; 1 or 2 cc. of the vaccine, which contained 100,000,000 bacteria, was injected every three days.

Twenty-four hours after the first injection, from 5 to 20 cc. of blood was withdrawn with a syringe containing 5 per cent solution of sodium citrate; the mixture was immediately injected into the buttock or under the skin of the abdomen of the infant.

The treatment was decidedly effective in the few cases reported.

SCHLUTZ, Chicago. [AM. J. DIS. CHILD.]

EXPERIENCE WITH ACETARSONE IN CONGENITAL SYPHILIS. BAUMBACH, Arch. f. Kinderh. **99**:151 (May 30) 1933.

This clinical report deals with the results observed in sixty-one infants with congenital syphilis who were treated with acetarsone by mouth. The series was divided into three groups. The first group received the rapid treatment with acetarsone, consisting of daily doses of the drug for six weeks at each course. The intermittent treatment with acetarsone, which was given to the second group, consisted of twelve week courses in which the drug was given for periods of one week alternating with periods of one week with no medication. The third group was treated by the combined method, in which mercurial ointment was administered by inunction for one week followed by acetarsone for one week, and the two methods of therapy were alternated for a total of twelve weeks. In all three groups rapid improvement in symptoms, physical signs of syphilis and general health occurred during the first few weeks of treatment. Serologically, the best results were obtained by the combined treatment, with which two thirds of the patients gave negative reactions to the Wassermann test after the first course. There were eighteen deaths—ten from pneumonia, three from sepsis, one from dyspepsia and four from the syphilitic infection directly. In no instance was any injurious effect attributed to acetarsone.

LEMASTER, Evanston, Ill. [AM. J. DIS. CHILD.]

INCUBATION TIME OF ERYTHEMA NODOSUM. DÉNES VON MÓRITZ, Arch. f. Kinderh. **99**:177 (May 30) 1933.

Three children with no history of contact with tuberculosis were admitted to the hospital and were found to have a negative reaction to tuberculin. In the hospital they were exposed to patients with open tuberculosis. Within from five to six weeks later, typical erythema nodosum developed in each of the three children, and the tuberculin test gave strongly positive results. These observations furnish further confirmation of the view that erythema nodosum is caused by tuberculosis and that erythema nodosum appears toward the end of the incubation period of tuberculosis when allergy to tuberculin arises.

LEMASTER, Evanston, Ill. [AM. J. DIS. CHILD.]

CHEMISTRY OF THE SKIN. A. LOEWY and G. CRONHEIM, Biochem. Ztschr. **256**:411, 1932.

Chemical analyses were made of the skins of rats and of guinea-pigs both under usual conditions and when the animals were under greatly reduced pressure, kept in the dark, irradiated with ultraviolet rays or treated with viosterol. The water and fat contents of the skin are highly variable even under normal conditions. The nonprotein nitrogen was not affected by five hours of ultraviolet irradiation or by exposure to one-half atmospheric pressure for periods up to eighteen days. It is difficult to judge the significance of such analyses in guinea-pigs, since even normally the nonprotein nitrogen ranges from 123 to 227 mg. per hundred cubic centimeters, but in the rat, in which the normal variation is from 86 to 114 mg., an increase of 27 per cent was found under reduced pressure and an increase of 36 per cent under the influence of viosterol. The chlorine content of the rat's skin was increased by low pressure or treatment with viosterol, but it was decreased in the dark or under ultraviolet irradiation. The potassium was raised by long sojourn at low atmospheric pressures or when viosterol was administered; it was lowered by ultraviolet irradiation but unaffected by darkness. The calcium was decreased under low pressures or by treatment with viosterol. The sodium was practically constant. The magnesium was increased by low pressure or by irradiation. In the guinea-pig, just as in the rat, the chlorine of the skin was affected. The potassium content was hardly determinable, but the amount was increased by radiation or by viosterol. The calcium was not affected by darkness or irradiation, and the influence of viosterol and of a low pressure was uncertain. So far as magnesium is concerned, the results showed great variability, except that the magnesium decreased markedly during fasting. Under irradiation, the ratio of cations to halogens in the rat and the guinea-pig was increased. In guinea-pigs, the cation content decreased during fasting.

KUGELMASS, New York. [AM. J. DIS. CHILD.]

FUNCTIONAL CHANGES OF THE THYROID IN FLORID SECONDARY SYPHILIS DETERMINED BY THE KOTTMANN REACTION. A. D. TROITZKAJA, Dermat. Wchnschr. **96**:709 (May 27) 1933.

Troitzkaja points out that, whereas in gummatous and congenital syphilis the endocrine glands may present gummatous or fibrous processes, secondary syphilis causes only temporary changes that do not lead to anatomic changes but are more of a functional character. Clinical observations often reveal an irritative swelling of the organ, but the functional changes are not so easily recognized. To determine the functional changes the author employed the Kottmann reaction, a photochemical colloid reaction, which indicates the functional activity of the thyroid by the dispersion capacity of the serum. Since women are more subject than are men to disturbances of the thyroid tests were made on 100 syphilitic women, of whom 15 were in the primary stage of syphilis and 50 in the beginning secondary stage and 35 had relapses. None of the patients had received treatment before the test. The results indicate that the spreading syphilitic infection involves the thyroid and that the impairment usually becomes manifest in a reduction of its functional activity, although its function may be increased in a small percentage of cases. The Kottmann reaction, in revealing the smallest functional changes, also proved that the swelling of the gland generally concurred with hypofunction and not with hyperfunction, as is the case in exophthalmic goiter. This concurrence of the swelling of the thyroid with hypofunction is the result of a temporary inflammation. The syphilitic character of the thyroid changes is proved by the efficacy of the antisyphilitic treatment.

[J. A. M. A.]

FOX-FORDYCE DISEASE. S. GRSCHEBIN, Dermat. Wchnschr. **96**:825 (June 17) 1933.

A woman, 25 years old, presented typical Fox-Fordyce disease involving the axillae. It had been present for four years. The only period during which

pruritus was absent was during the course of a pregnancy which ended two months before examination. The pruritus recurred three or four weeks following the delivery.

HEMORRHAGE AND IMPAIRMENT OF THE BLOOD AFTER ARSPHENAMINE. S. EMANUEL, Dermat. Ztschr. **67**:24 (July) 1933.

A woman, 27 years of age, was treated for a tertiary syphilid. During the fourth course of antisyphilitic therapy, a universal purpura developed. Six days later she died. The author reviews the literature in regard to this complication of therapy with arsphenamine.

L. TAUSSIG, San Francisco.

PATHOGENESIS OF BAKERS' ECZEMA. N. VAN VONNO and J. STRUYCKEN, Dermat. Ztschr. **67**:43 (July) 1933.

Van Vonno and Struycken point out that, in spite of a decreased consumption of flour and bread, bakers' eczema is increasing. They think that this incongruence can be explained by the increase in allergic disorders. Because some investigators have ascribed the recent increase in bakers' eczema to the substances that are added to the flour to make it more suitable for baking, they made tests on bakers with and without eczema and on controls. In experiments with various types of wheat, rye and rice flours, they gained the impression that one of the main causes of the predisposition to eczema exists in wheat flour. They made tests with various substances that are added to the flour to make it more suitable, but they reached the conclusion that these substances, particularly ammonium persulphate, are not responsible. In discussing the treatment, they point out that some advise a change of occupation for bakers who are subject to eczema; but since this is not always possible, they recommend tests to determine to what type of flour the patient is susceptible and, after the eczema has been cured, treatment by desensitization. They call attention to errors and wrong conclusions in the studies of the investigators who considered the addition of ammonium persulphate as the main cause of bakers' eczema, and they point out that bakers' eczema was known long before this substance or any other was ever added to the flour and that consequently it is unnecessary to prohibit the use of these substances.

[J. A. M. A.]

EPIDERMAL CYSTS FOLLOWING INJECTION OF VIOSTEROL. H. SANDER, Virchows Arch. f. path. Anat. **289**:190, 1933.

Epidermal cysts developed at the site of injection of viosterol into a vein of the ear in thirteen of twenty-two rabbits. The cysts were derived from hair follicles and sebaceous glands. Ergosterol that had not been irradiated did not have a similar effect.

SCHULTZ, Evanston, Ill. [ARCH. PATH.]

SKIN TURGOR OF SUCKLINGS. H. PAFFRATH and W. RIECKE, Ztschr. f. Kinderh. **54**:380, 1933.

This is the description of an apparatus for measuring skin turgor. The principle of the apparatus consists in measuring the retraction force (elasticity) of a fold of skin of certain size, the force being registered graphically.

SKIN TURGOR IN NUTRITIONAL DISTURBANCES. W. RIECKE, Ztschr. f. Kinderh. **54**:385, 1933.

The skin turgor of fifty children with acute and chronic nutritional disturbances was found to be below normal. The lowest values were observed in cases of intestinal intoxications, but cases of dyspepsia without intoxication also showed low values. Weight and skin turgor are not always parallel; improvement in turgor usually precedes the hydration of the subcutaneous tissues.

SHELLING, Baltimore. [AM. J. DIS. CHILD.]

A Fatal Case of Hemangioma Cavernosum Congenitum. A. S. Pettersson and R. Romanus, Acta pædiat. **14**:417 (April 28) 1933.

At birth the infant showed a large cavernous hemangioma, which formed a tumor on the left shoulder. The tumor increased in size and spontaneous ecchymoses developed, causing the patient to be admitted to the hospital at the age of 2 months. Roentgenograms showed symmetrical invasion of the superior mediastinum. Stridor, cough and cyanotic attacks appeared and increased in severity. The patient died at 5 months of age of bronchopneumonia. At autopsy, the tumor, histologically benign, was found to have invaded the thoracic cavity by extension, displacing the thymus upward and greatly compressing the primary bronchi.

McIntosh, New York. [Am. J. Dis. Child.]

The Sodium Chloride Metabolism in Patients Suffering from Epidermolysis Bullosa Dystrophica. M. K. Polanǫ, Nederl. tijdschr. v. geneesk. **76**:4207 (Sept. 3) 1932.

A diminution in the renal excretion of sodium chloride is described in two patients, aged 14 and 17, suffering from epidermolysis bullosa dystrophica. This diminution should be regarded as a symptom of the disease to be found in generalized cases. No influence on the course of the sickness could be found by the administration of a diet containing great quantities of sodium chloride or of one containing no sodium chloride.

van Creveld, Amsterdam, The Netherlands. [Am. J. Dis. Child.]

Society Transactions

CLEVELAND DERMATOLOGICAL SOCIETY

J. R. Driver, M.D., *Reporter*

Regular Meeting, Sept. 28, 1933

Sidney Littman, M.D., *Presiding*

Tertiary Syphilis: Bilateral Total Eighth Nerve Deafness. Presented by Dr. H. F. De Wolf.

A white man, aged 26, from the service of Dr. Cole and Dr. Driver at Cleveland City Hospital, began in 1930 to have periods of deafness, which lasted from one to several days, usually following exposure to cold, and since June, 1933, he has been totally deaf. There is no history of deafness in the family. There is a history of a chancre in the patient in 1928. He was given no antisyphilitic treatment, however, until 1931, when he received fifteen intravenous and eight intramuscular injections.

Physical examination revealed a mottled condition of the skin over the trunk, which the patient states has always been present. Examination revealed no other abnormalities.

The Wassermann and Kline tests of the blood were four plus on two occasions. Examination of the spinal fluid yielded negative results. The urine was normal. The blood count was normal. Treatment has consisted of four injections (210 mg.) of aminohydroxphenyl arsenoxide between September 15 and 25 and 2 Gm. of potassium iodide daily since September 15. No improvement is observed.

Late Secondary Syphilis: Iritis and Paralysis of the Right Fifth, Seventh, Eighth, Eleventh and Twelfth Cranial Nerves. Presented by Dr. H. F. De Wolf.

A Negro, aged 33, was admitted to the service of Dr. Cole and Dr. Driver at Cleveland City Hospital on Sept. 13, 1933. The patient stated that his health had been good prior to 1930, when he acquired syphilis. Four or five months after the appearance of the penile lesion his eyes became red and painful, and a diagnosis of syphilitic iritis was made. He received six intravenous injections and mercury rubs over a period of two and one-half months, which resulted in rapid control of the ocular complaint. His eyes were normal until Sept. 1, 1933, when he began to have redness and burning of the right eye, with pain generally over the right side of the face, neck and shoulders and loss of vision. General physical examination revealed nothing abnormal except the scar of the lesion on the glans penis.

Ophthalmologic examination revealed that the right pupil was miotic, irregular and fixed because of the numerous adhesions. The cornea was cloudy, with moderate circumcorneal injection. The vision in this eye was practically gone. The left pupil had been dilated with atropine, but was irregular, owing to old adhesions. Neurologic examination revealed paralysis of the right fifth, seventh, eighth, eleventh and twelfth cranial nerves. There was some paralysis of the right upper extremity.

The Wassermann and Kline tests of the blood were four plus on two occasions. Examination of the spinal fluid yielded negative results. The urine was normal. A blood count gave normal results.

Treatment has consisted of compresses of warm boric acid to the eyes; a 1 per cent solution of atropine sulphate to the eyes; potassium iodide, 2 Gm. daily; three

injections of thiobismol, 0.2 Gm. each, since September 16, and two injections (90 mg.) of aminohydroxphenyl arsenoxide since September 23. No appreciable improvement has occurred.

SECONDARY SYPHILIS: ACUTE SYPHILITIC MENINGITIS. Presented by DR. H. F. DE WOLF.

A Negro, aged 22, was admitted to the service of Dr. Cole and Dr. Driver at Cleveland City Hospital on Sept. 20, 1933. The patient gave a history of measles in 1919, mumps in 1921 and pertussis in 1924; otherwise there were no illnesses until three months ago, when he had a chancre, for which he has received only local treatment. On Sept. 12, 1933, he became ill with fever, malaise, vomiting, pain in the head and stiff neck. He was admitted to the division for contagious diseases on September 16, with a tentative diagnosis of cerebrospinal meningitis; he was transferred to the dermatologic service.

Physical examination revealed a poorly nourished young Negro, not acutely ill. Typical syphilitic adenopathy of the left inguinal region was present. Over the chest and back were a few scattered areas of depigmentation. Over the plantar surface of the feet were healing syphilids. Otherwise examination of the skin and mucous membranes gave negative results. The patient had fever averaging about 38 C. (100.4 F.) and rising at times to 39 (102.2 F.). Examination of the spinal fluid revealed 920 cells per cubic millimeter; 95 per cent of the cells were mononuclears; the Pandy test was four plus and the Wassermann test, four plus. The blood count revealed: red cells, 4,600,000; white cells, 7,000; hemoglobin, 80 per cent. The differential count was normal. The Wassermann and Kline tests of the blood were four plus. Examination of the urine showed a trace of albumin and an occasional leukocyte.

Treatment has consisted of three injections of thiobismol, 0.2 Gm. each; potassium iodide, 2 Gm. daily, and the injection of 20 mg. of aminohydroxphenyl arsenoxide. Symptomatically, the patient is much improved but is still febrile.

DISCUSSION

DR. H. N. COLE: It is unfortunate that dermatologists in America do not discuss syphilis more often at meetings, especially syphilis as it is related to internal medicine. One never picks up the proceedings of the French Dermatological Society without finding four or five different reports on syphilis of the brain or other internal organ. It would be a good plan if it were arranged for dermatologists to show more cases of this sort at their meetings. Syphilis is included in our work but ignored too much at our meetings.

These three cases present interesting involvements of the central nervous system, and, incidentally, two of the three patients are Negroes. So much is said these days of the low incidence of involvement of the central nervous system in the colored race. One rarely sees a Negro with meningitis of this type. It is not uncommon for meningitis to occur after the patient has come to the clinic and received a few injections of an arsenical and perhaps a few injections of other heavy metals and then lapsed. It is not uncommon for a patient with this type of case to be brought into the hospital in an ambulance, unconscious; it is then necessary to make a diagnosis, perhaps between meningitis, diabetes, fracture of the skull and several other possibilities.

Cases of this sort are explained as due to the patients having had no opportunity to build up natural resistance. The disease relapses, and they are overwhelmed. The patient under discussion, however, is not of this type. He has never had therapy. He certainly has had every opportunity to build up natural resistance, yet he apparently lacks it entirely. I have seen few instances of this type of syphilitic meningitis—certainly not with a cell count of 920 cells per cubic millimeter. The patient was seen by the officer who admitted him. He had a high fever, was quite sick and had a stiff neck and a masklike expression; the officer diagnosed the condition as epidemic encephalitis and sent him to the hospital for

contagious diseases. Only after an opportunity was given to study the condition thoroughly was it possible to make the correct diagnosis of acute syphilitic meningitis.

The other Negro presents a striking example of a relapse following slight therapy. The relapse, probably vascular in type, involved the fifth, seventh, eighth, eleventh and twelfth cranial nerves. Three years ago the patient received six injections of an arsenical and mercury rubs over a period of two months. In a study made by five cooperating clinics (*Ven. Dis. Inform.* **12**:55, 1931), relapses were found to occur more frequently in cases in which therapy of less than twenty injections of an arsenical and twenty injections of a heavy metal had been given. Thus one can easily understand why this patient was prone to relapse. His period of relapse came somewhat later than the average period reported in this cooperative study, that is, nine months after the last injection.

The white man also presents an example of relapse with bilateral involvement of the eighth nerve. I am interested in the prognosis. The fact that the patient has had the involvement for such a long time precludes in my estimation, much in the way of a return of hearing. Probably such severe damage has been done and so much fibrosis has ensued that one can hope for little in the way of a return of hearing.

DR. H. F. DE WOLF: I am interested in the patient with the total deafness and in the patient with the paralysis of the right cranial nerves, as both showed a normal spinal fluid on examination. One expects to find evidence of syphilis in the cerebrospinal fluid. I asked the neurologists to see both patients, and they found the absence of this evidence in the spinal fluid extremely difficult to explain. The syphilitic changes must be extradural.

DR. R. E. BARNEY: In the case of the white patient who shows involvement of the eighth nerve, probably syphilitic meningitis with edema of the auditory nerve occurred. The auditory nerve is enclosed in a bony casing, and by the time the spinal fluid is examined, the meningitis has run its course; and there are no findings in the spinal fluid. However, it is rather difficult to explain the case showing multiple involvement of the cranial nerves.

LUPUS VULGARIS WITH CARCINOMATOUS DEGENERATION. Presented by DR. H. F. DE WOLF.

A white man, aged 49, from the service of Dr. Cole and Dr. Driver at Cleveland City Hospital, had enjoyed good health until the onset of the present cutaneous disease. During the World War he was wounded by shrapnel on the left side of the neck and on the left shoulder. There is no history of tuberculosis or cancer in the family. In 1922, a small papule appeared on the right side of the neck, and the patient was given three roentgen treatments at Lakeside Hospital. The lesion increased, and new lesions appeared on the left side of the face, forehead, shoulders, back and thighs. From time to time since April, 1924, the patient has been under treatment at the Cleveland Clinic, where he is irradiated with grenz rays. In January, 1929, a squamous cell carcnoma was removed from the right side of the face, and a skin graft was performed. In March, 1933, a second ulcerated lesion appeared on the right side of the neck.

General physical examination gave negative results. Over the right side of the face and encircling the neck, except for the middle of the posterior aspect, was an extensive confluent lesion, consisting of scarring, atrophy and reddish-brown, scaly, slightly elevated papules at the periphery. On the right side of the neck there was an ulcerated, bright red, circular lesion, the size of a half-dollar. Just anterior to and slightly above the lesion there was a smaller ulceration of the same nature, about 1 cm. in diameter. An occasional keratotic lesion was noted, and there were smaller atrophic and scarlike lesions on the left side of the forehead, the left side of the chin, the posterior portion of the left arm near the axillary fold, the left lumbar region and the anterior aspect of the right thigh. Otherwise, general physical examination revealed nothing abnormal. The patient is afebrile.

A section taken for biopsy from the ulcerated lesion on the right side of the neck showed that the epithelium was markedly acanthotic, especially in the layer of prickle cells. There was parakeratosis. The basement was intact. The corium was vascular and showed some areas of hemorrhage. The stroma of the corium was largely displaced by a fairly dense cellular exudate with strands extending far down into the corium. The nuclei of invading cells were large and vesicular and showed fairly frequent mitoses. The cytoplasm was abundant and acidophilic but ill defined. Only scattered inflammatory cells, chiefly lymphocytes, were present. A diagnosis of carcinoma simplex was made.

No therapy has been given as yet.

DISCUSSION

DR. H. N. COLE: One sees few cases of this type here, as compared with European countries, where there are a large number. Malignant growths developing on old sites of lupus vulgaris that have been treated with roentgen rays, are of a low grade of malignancy, possibly owing to the fact that in most cases there is radiodermatitis with fibrosis, which prevents the cells from disseminating. One therefore does not expect early involvement of the lymph nodes. In lupus vulgaris even without radiodermatis one occasionally finds malignant developments on the scars. It seems, however, that we see more malignancy in cases in which radiation is used. It is certainly justifiable to use radiation in the treatment of the disease, for it is a most difficult condition to cure. Excision can be used if one does not have to cut too deeply, but one hesitates to use grafts of full thickness in such a case for fear of leaving a few malignant cells in the graft. I am more in favor of using desiccation or curettage and interstitial irradiation with radium needles. The interstitial use of radiation does not seem to have the same effect as surface irradiation. The plan is to use interstitial radiation with platinum-radium needles, and to present the patient at a later meeting.

NEW ENGLAND DERMATOLOGICAL SOCIETY

J. HARPER BLAISDELL, M.D., *Secretary*

Regular Quarterly Meeting, Oct. 11, 1933

RUDOLPH JACOBY, M.D., *Presiding*

PSORIASIS (?), DERMATOPHYTOSIS (?), KERATOSIS BLENNORRHAGICA (?). Presented by DR. BERNARD APPEL.

A white man, aged 56, a druggist, had an eruption on the extremities and trunk for twelve weeks prior to presentation. It started as scaly, itchy lesions on the soles and spread slowly to involve the feet, trunk, axillae and hands. The patient also had arthritis at the time of presentation.

Examination revealed sharply outlined, scaly, hyperkeratotic lesions involving almost the entire soles. Over the hands (on the backs only) were large, rupial lesions, the size of a coin, some of which were heaped up about one third of an inch. Over the front and back of the trunk were lesions almost classically psoriasiform, sharply outlined, annular and scaly.

The Wassermann test and urinalysis gave negative results. The blood smear showed moderate secondary anemia, with 4,000 white blood cells; otherwise it was normal.

The most probable diagnoses are given in inverse order. The diagnosis of keratosis blennorrhagica is consistent with the lesions on the soles, but not with those on the trunk and in the axillae. If that diagnosis is made, one would

probably have to make another diagnosis of the typical psoriasiform lesions also found on the trunk and in the axillae. The condition is accompanied by arthritis; however, the infrequent association of keratosis with gonococcal arthritis is not demonstrated in this case, as true gonococcal arthritis is usually nonarticular. Here the arthritis is bilateral and involves both legs and both knees. The other possible diagnosis is dermatophytosis; the onset of this condition is not inconsistent with epidermatophytosis, having started apparently as fine vesicles on the soles, which then developed into these scaly lesions and shortly afterward formed thick and hard keratotic, superimposed masses which have been softened and removed. There is, nevertheless, inconsistency with the rest of the lesions seen on the body. It is possible, of course, that the psoriasiform lesions on the trunk might be dermatophytides. Rupial lesions on the back of the hands are not consistent with the usual type of dermatophytides. At any rate, the condition would have to be explained as a direct secondary infection. In such a case, one would certainly not expect further involvement of the palms, which this patinet does not show. The third possibility is psoriasis. It seems to me that the general picture here is consistent with psoriasis, although the rupial lesions are certainly not those commonly seen; and the fact that the patient has no marked lesions on the elbows or knees is against it, although one knee does show some scaling. That there are no lesions on the scalp is also against the diagnosis of psoriasis, but the lesions of the nails and soles, which might be explained by the so-called pustular psoriasis, and the lesions in the axillae and groin are consistent with that diagnosis. The bulk of evidence, I think, is in favor of psoriasis.

Dr. Rudolph Jacoby: I favor the diagnosis of keratosis blennorrhagica, although no mention is made of gonorrhea in the history. My impression is that this patient has probably had psoriasis for some time, which could account for the involvement of the nails and the psoriasiform lesions, but the heaped-up, scaly, keratotic lesions are similar to those in a case which I recently saw, in which a man had acute gonorrhea followed by polyarthritis. During the period of treatment for the arthritis, horny, keratotic, conical lesions developed in various areas over the body. The lesions began as small vesicles, the capsules of which cornified, with resulting cone-shaped horns varying in size from ¼ by ¼ inch to 1 by 1 inch (0.6 by 0.6 cm. to 2.5 by 2.5 cm.). He was treated with specific gonococcus vaccine, and the cutaneous lesions cleared up with the arthritis.

Dr. Edward W. Karcher: I think that this patient should have a complement-fixation test. If this is a systemic gonococcic infection, the patient ought to have such a test.

Dr. Bernard Appel: That was done. The question came up about the Schwartz-McNeil test. Dr. Hinton told me that in his opinion the test was not of great value, but that the state laboratory continued to do it because many men still relied on it and requested it. The test is subject to many false positive and negative interpretations. My impression, therefore, is that the complement-fixation test of the blood is not sufficiently specific to be of value in the general run of cases.

Dr. Joseph Muller: In trying to make a diagnosis of a case, one must consider not only the lesions of the patient's skin but the entire condition. Here is a patient who looks sick and who has a low fever, varying between 99.6 and 100 F. There is a history of arthritis of two years' duration with, first, involvement of one of the joints, and later, at the time when the eruption started, involvement of two more joints. The patient also looks anemic. The eruption on the trunk looks like psoriasis. At the same time the eruption of the leg is hardly consistent with this condition, and rupia-like lesions must be sparse in psoriasis. The rupia-like lesions seen on the hands are common in keratosis blennorrhagica. Similar lesions may also appear in syphilis. They are seldom seen. If one diagnosis is to be made, and not two or three, I think that we shall have to make a diagnosis of keratosis blennorrhagica, for the gyrate eruption, which is like psoriasis on the body, is consistent with a lesion often seen in such cases. The appearance of the feet is typical of keratosis blennorrhagica.

DR. EDWARD W. KARCHER: A smear should be made of the prostate gland, as that would be the focus of infection.

DR. NELS A. NELSON: I think that the complement-fixation test is not looked on very highly from a diagnostic point of view in acute gonorrhea. Many physicians use it as additional presumptive evidence in chronic gonorrhea. I think that a complement-fixation test in this case would do no harm.

DR. FENNER A. CHACE: The whole picture seems to fit better into an atypical psoriasis than anything else. This is certainly not typical.

DR. J. H. SWARTZ: I am inclined to favor a diagnosis of psoriasis. I think that a biopsy would be very much in place.

DR. FRANCIS P. MCCARTHY: I think that examination of the bacteria and fungi of the lesions on the soles would be helpful. I strongly advise the therapeutic use of gonococcus vaccine. I also advise an examination of the lesions for gonococci. As the patient has a fever, I suggest that blood cultures be taken. I am in favor of the diagnosis of psoriasis in this case, and I believe that the lesions are somewhat altered by the persistent edema that is present in both legs. The feet are moist and soggy, which also alters the picture.

DR. J. H. SWARTZ: I do not think that a therapeutic test with gonococcus vaccine will rule out psoriasis, since the lesions may improve as a result of nonspecific therapy.

DR. FRANCIS P. MCCARTHY: Gonococcus vaccine is one of the most specific vaccines available in the treatment of arthritis. Many years ago, while serving in the hospitals in the Canal Zone. I treated a large number of cases of gonococcic arthritis in Negroes. Stock gonococcus vaccines had no effect, but the laboratory was able to make up a vaccine which gave wonderful results. As for the effect of gonococcus vaccine in the treatment of psoriasis, it seems to me that one would have to use large doses to get a nonspecific protein therapeutic effect.

DR. C. GUY LANE: Barber discussed not only pustular psoriasis but the acrodermatitis continua of Hallopeau. I think that the condition around the nails and feet in this case is not unlike that in one or two cases that have been presented before this society, in which the diagnosis of acrodermatitis continua was made. I also saw one or two cases of pustular psoriasis that Barber showed. While they did not fit exactly into the picture which this patient shows now, I believe that as a possibility here one ought to consider acrodermatitis continua and, secondarily, a type of pustular psoriasis.

Barber stated that he found tar preparations helpful in the treatment of pustular psoriasis.

DR. FRANCIS P. MCCARTHY: Two minims of stock typhoid vaccine administered intramuscularly will produce a violent chill, often associated with a herpetic eruption and a high fever. I know of one death from this form of therapy among a group of cases of arthritis that I treated several years ago. The condition of these with the chronic arthritis was improved, and the joints were loosened, possibly mechanically, by the chills. The subacute conditions were greatly improved and the cases of acute arthritis were markedly improved. I should not advise typhoid vaccine in this case.

DR. BERNARD APPEL: Salicylic acid and sulphur ointment, applied in moderate amounts, caused marked improvement in the lesions which, before the ointment was applied, were thick, crusty and scaly. They softened after the use of the ointment. The patient is not under any active treatment. I saw him in consultation with his family physician, who is treating the arthritis with intravenous injections of streptococcus vaccine. Certainly the polyvalent strain of streptococcus, made into vaccine and given in gradually increasing doses, apparently had little effect on this patient.

DR. JOSEPH MULLER: I believe that chrysarobin ought to clear up the lesions on the chest, if the condition is psoriasis.

BASAL CELL CARCINOMA. Presented by DR. E. LAWRENCE OLIVER.

A white boy, aged 18, a warehouse worker, had a lesion on the right cheek for four years, which increased slowly in size. There was no bleeding at any time.

Examination revealed a lesion, the size of a quarter, slightly raised and partially composed of small nodules the size of a split pea, slight atrophy between the nodules and telangiectasis. The border was sharply demarcated, with a somewhat pearly appearance. The lesion was slightly lighter in color than the surrounding skin.

The report of the biopsy was "basal cell carcinoma."

The treatment suggested was either roentgen or radium.

DISCUSSION

DR. C. GUY LANE: This is an unusual case occurring at this age. The previous cases that I have seen in patients about 20 years of age have followed trauma, usually in indistinctly blond or light-colored persons.

DR. FRANCIS P. MCCARTHY: I have looked at these slides and agree that the growth is a basal cell epithelioma. Dr. Mallory believes that most of these tumors arise from the hair matrix and he makes a diagnosis from the character of the cells. The arrangement of the cells in this case is in the form of deeply staining, elongated epithelial cells occurring in whorls around the hair follicles. It occurred to me that this type of basal cell tumor may begin early in life and have its origin in a nevus, and that trauma may be the exciting factor in the growth of the tumor.

DR. WALTER T. GARFIELD: At the City Hospital was a young Chinese girl with a lesion on the flank, which was removed. According to the pathologist, it was a basal cell carcinoma, originating from the sweat glands. I thought that was getting down to a fine point in diagnosis.

DR. ELLWOOD C. WEISE: I should like to mention a similar case, that of a boy, aged 19, who had a lesion on the upper eyelid, which he said began as a small "pimple" which he continually pricked with a needle. It was proved by biopsy to be a basal cell carcinoma and responded well to treatment with radium.

MAJOCCHI'S DISEASE (PURPURA ANNULARIS TELANGIECTODES). Presented by DR. E. LAWRENCE OLIVER.

A white girl, aged 8, presented an eruption that began during the summer of 1933 after swimming, and was present for three months before presentation. There had been itching at times. The eruption began as small discolorations on the feet, which gradually grew in size and became somewhat pale. Other irregular patches appeared on the lower part of the legs subsequently.

Examination revealed round, pigmentary, purpuric maculae, with clear centers, on the dorsal surface of both feet. The borders showed a certain amount of telangiectasis. There was an accentuation of the follicles of the hairs in these regions. A complete physical examination gave negative results.

The hemoglobin was 70 per cent, with 6,400 white blood cells and a normal differential count. The biopsy report was "chronic inflammation."

The patient had received no treatment.

DISCUSSION

DR. BERNARD APPEL: I think that Majocchi's disease in a very early stage is the most probable diagnosis. This case does not show any marked, purplish, definitely developed telangiectases or the central ulceration which is common in these well developed cases. There is definite purpura and a deposit of blood pigment in annular forms. It is obviously not Schamberg's disease or angioma

serpiginosum, the two other common diseases with which Majocchi's disease might be confused. By elimination, therefore, this is probably an early stage of Majocchi's disease.

DR. J. H. SWARTZ: I agree with the diagnosis.

POWDER BURNS. Presented by DR. M. RYAN.

A white boy, aged 15, stated that on July 4, 1933, a cannon exploded and powder flew on his face, neck and hands. The patient showed blue pigmented spots involving the right side of the face and neck and the right ear. Similar spots were present on the hands and arms. The patient had received no treatment.

DISCUSSION

DR. J. HARPER BLAISDELL: It seems to me highly inadvisable to attempt any treatment in this boy. Gunpowder is present in large amounts well down in the skin. If you remove mechanically all those powder grains, you will replace them with a scar which will be much whiter than his normally dark skin. From a cosmetic point of view, I think that it would be substituting one trouble for another.

DR. E. LAWRENCE OLIVER: I agree with Dr. Blaisdell. I think that treatment is hopeless as regards any improvement. The proper treatment is to give general anesthesia at the time of the accident, and to scrub out the foreign material thoroughly with a stiff brush. I do not think that this method is generally known by the members of the profession at large.

I do not think that the powder would be likely to cause any malignant change.

PITYRIASIS RUBRA PILARIS. Presented by DR. C. EDWARD GREENE.

A white man, aged 48, a laborer, stated that six weeks prior to presentation, he had struck his leg, after which an eruption had appeared which spread over the skin and to the other leg. He did not realize that a papular eruption existed over the rest of the body. He had treated the condition at home with hot water applications and dry protective bandages. The lesions in the palms, he thought, were caused by using his pick and shovel.

Examination revealed multiple discrete follicular papules, each with a superimposed horny plug. A hair could be seen emptying from each papule. Near the knees, a linear group of the papules gradually emerged into the encrusted, scaly areas on the legs. The lesion in this region had a peculiar red base with a piling up of silvery scales and crusting, resembling psoriasis. There was a psoriatic lesion in each palm, and the soles were fissured and somewhat scaly, although the latter condition had cleared up fairly well after two and one-half weeks in bed. The eruption was also noted at the shaft of the penis.

Biopsy showed infiltration of lymphocytes, with a down growth of rete pegs and horny epithelial plugs.

The patient received irradiation with ultraviolet rays and local applications, with subsequent diminution in the size of the papules.

DISCUSSION

DR. E. LAWRENCE OLIVER: I think that we can consider two diagnoses here: (1) psoriasis and (2) streptococcic dermatitis. In some places there are rather thin scaling areas, like cigaret paper, with sharply defined edges. I think psoriasis is the more probable diagnosis. The lesions on the palms would fit into that diagnosis better. The absence of psoriasis elsewhere would not rule it out, but might make it a little improbable. I saw nothing in particular to suggest pityriasis rubra pilaris. If he had that disease, I do not see how it could have cleared up so rapidly, as it seems to have done on the trunk.

DR. J. HARPER BLAISDELL: I can see nothing at the present time that suggests pityriasis rubra pilaris. The hair follicles on the backs of the fingers

are normal, and the lesions on the lower part of the legs, from their crusts and progressive character, indicate some sort of secondary infection. In some ways it reminds me of ecthyma.

DR. AUSTIN CHEEVER: I cannot see any sign of pityriasis rubra pilaris in this patient, and I believe as Dr. Oliver does, that the condition is very likely a streptococcic dermatitis.

DR. M. RYAN: I think that the condition on the hands is typically psoriatic.

DR. WILLIAM P. BOARDMAN: There are marked hyperkeratotic follicular lesions with broken-off hairs on the body and extremities. Frequently in pityriasis rubra pilaris lesions resembling psoriasis occur on the extremities. One cannot explain this follicular eruption by psoriasis, but one can explain the psoriatic lesions by pityriasis rubra pilaris. A simple lichen pilaris would not occur in those situations. I do not think that there has been any change on the legs since the patient was admitted.

DR. MAURICE J. STRAUSS: I do not think that this is a case of pityriasis rubra pilaris.

TRAUMATIC ULCER (RIGHT LEG); LATE SYPHILIS; TINEA VERSICOLOR. Presented by DR. LORETTA J. CUMMINS.

A white man, aged 42, an Italian, a cook, had an ulcer on the right ankle, on both medial and lateral surfaces, for two years. "Vaseline oil" was injected into the ankle in 1917, in order to avoid further war service. This produced considerable swelling, but did not incapacitate him. About two years prior to presentation, an ulcer appeared over each malleolus, and he had more or less pain thereafter. The patient had gonorrhea and a penile sore in 1916, for which he received twenty injections in the arm. He had fifteen injections of bismuth salicylate without improvement of the condition in the ankle. The last blood test was strongly positive. Since admission, several small pieces of paraffin had come out of the sinus. He had a rash over the chest, shoulders and back seven or eight years previous to presentation, with an exacerbation every summer.

The right ankle was found to be moderately swollen and firmly edematous. On the inner aspect was a roughly rectangular ulcer, 6 cm. long and 3.4 cm. wide. At the upper end, which was pointed, there was an area of scar tissue of approximately equal size, all sharply delineated. There was a small ulcer 0.7 by 1 cm. in diameter; several small scars were noted above this. On the lateral side were two distinct ulcerations, one anteriorly (3 by 1.5 cm.) and one posteriorly (4.5 by 1.3 by 0.5 cm.). Surrounding these was an area of scar tissue approximately three times their size and sharply delineated. Below the malleolus was an epithelialized sinus with an opening, 0.3 by 0.4 cm. in size. All the ulcers were sharply outlined, shallow and fairly clean, with red bases. The eruption on the chest and back was light brown to yellow, made up of confluent areas, slightly raised and covered with a fine fuzzy scaling. There were inguinal and epitrochlear glands and a penile sore, and the heart was found to be slightly enlarged, with a systolic murmur.

Urinalysis gave negative results except for an occasional hyaline and granular cast. The blood count showed a normal hemoglobin value and red cell count, 12,400 white cells and a normal differential count. A preparation in potassium hydroxide of scales from the back showed tinea versicolor and fungi. The Wassermann reaction of the blood was strongly positive. The Hinton test was positive on Sept. 12, 1933.

The patient had received potassium iodide and a mercury preparation previous to the administration of bismuth salicylate, but no other antisyphilitic therapy. The ulcers had been given cysteine therapy. The tinea versicolor had been treated with sodium thiosulphate, 20 per cent, externally. The patient was still receiving potassium iodide. The treatment with cysteine was begun on Sept. 22, 1933. The patient was also receiving stimulating doses of ultraviolet rays.

DISCUSSION

DR. AUSTIN W. CHEEVER: I obtained two different histories from the patient: (1) that the ulcers had never healed; (2) that the old ulcers had healed and then fresh ulcerations had occurred in the scar tissue. This seems extremely unlikely in late syphilis. I think that probably the condition is due simply to the injections of oil in a patient who has had syphilis.

DR. WILLIAM P. BOARDMAN: I agree that this is probably not a syphilitic ulcer on the leg, but I think that it may have been modified by syphilis. Several of the borders are circinate, but there are an overhanging edge and deep-seated, adherent scars which do not look like syphilis. I cannot explain the gyrate border by the oil alone. I think that there may have been a syphilitic factor in addition which gives it that characteristic.

DR. C. MORTON SMITH: I cannot believe that the present condition is due to late syphilis. Apparently the ulceration involves scar tissue of the previous ulceration, said to have been caused by an injection of paraffin oil. It is unusual for a syphilitic ulceration to occur in the scar of a previous syphilitic ulcer. It seems to me that an important point is whether a factitious element is present. Is there any motive for self-inflicted trauma? I believe that this question should be carefully considered in the light of the previous malingering.

BRONX DERMATOLOGICAL SOCIETY

HENRY SILVER, M.D., *Secretary*

Regular Meeting, Nov. 23, 1933

SAMUEL FELDMAN, M.D., *President*

POIKILODERMA-LIKE CONDITION OF THE SOLES (SEQUELAE OF EPIDERMOLYSIS BULLOSA). Presented by DR. PAUL GROSS.

J. U., 61 years old, born in the United States, gave a history of having an infection on the feet twenty-five years ago, which was treated by a physician with freezone and scraping of the skin of the soles. Up to that time the patient had been a life-guard. Further questioning brought out the fact that he has had blistering of the hands and feet since early childhood. The outbreaks are confined to the warm weather. Local treatments have no effect. The family history revealed that the mother and father were first cousins. No other member of the family is similarly affected.

When the skin was examined, the most pronounced changes were on the sole of the left foot and consisted of a diffuse atrophy with scleroderma-like patches and other areas of cigaret paper-like atrophy. There were also telangiectasia and pigmentation. In the middle of the sole was a crusted patch. After the crust was removed, a red surface covered with a thin epidermis was seen. The lesion was tender. There was a band of hyperkeratosis on the plantar surface of the big toe, and the points of pressure on all the toes presented circumscribed, callus-like lesions. The same condition, but less pronounced, was present on the right sole.

The Wassermann test of the blood and the results of urinalysis were negative. Roentgen examination of the feet revealed no abnormalities.

DISCUSSION

DR. P. GROSS: The involved areas bear a close resemblance to those in radiodermatitis, but there is no history of roentgen therapy having been given. The patient, however, gives a history of repeated attacks of vesicles and bullae

on the palms and soles during the summer months since childhood. With that history in mind I thought of epidermolysis bullosa.

DR. C. WOLF: Though the patient has had this condition all his life he shows no evidence of epidermolysis bullosa such as the appearance of lesions following trauma. The clinical appearance suggests a burn following the use of carbon dioxide snow. The patient claims to have used freezone locally on the palms and soles.

DR. V. A. CORNELL: I accept the diagnosis as presented.

DR. M. BERKOVSKY: To correct any misunderstanding that may occur because of the use of freezone, I want to point out that there is no carbon dioxide snow in that proprietary. It is merely a popular remedy, used for corns and callosities, which contains salicylic acid in collodion.

DR. G. J. SPINNER: Clinically, it is impossible to make a diagnosis of epidermolysis bullosa. I suggest a biopsy.

DR. S. FELDMAN: The soles present lesions that resemble an atrophy following roentgen therapy. I know of no other agent that would produce a similar clinical picture. A biopsy would not aid us in making a diagnosis of epidermolysis bullosa.

DR. P. GROSS: I am sure that the lesions are not due to trauma or to medication. The patient was a life-guard and was constantly exposed to the hot sand and sun. The history is suggestive of epidermolysis bullosa. I should like to see the patient again in the summer and observe the type of bullous lesions.

BROMODERMA (?). Presented by DR. FRANK E. CROSS.

A man, aged 77, a porter, came to the Stuyvesant Square Hospital presenting vegetating hyperkeratotic lesions which varied in size from that of a bean to that of a walnut and were situated on the inner and outer surfaces of the ankles. Two large lesions were seen directly over the inner malleoli. The lesions were moderately firm, hemispherical and well defined. The eruption has persisted for the past three months.

The results of the physical examination and the past history are negative. The patient says that he has not taken drugs. The urine was tested for bromides and iodides and reported normal. The Wassermann reaction of the blood was negative.

For the past two weeks the patient has received 100 cc. of physiologic solution of sodium chloride intravenously three times a week, but to date he has shown little improvement.

The histologic examination corroborated the clinical diagnosis of bromoderma.

DISCUSSION

DR. P. E. BECHET (by invitation): When we first saw the patient we agreed that the case was one of bromoderma even though the patient said that he had not taken drugs. We could not detect bromides in the urine. The Wassermann and Kahn tests were negative. Clinically, the condition still impresses me as being bromoderma.

DR. S. PECK: I should like to examine the tissue. My reason is that Dr. Eller presented a similar case of proved iododerma in which the histology resembled closely that of mycosis fungoides.

This condition usually cannot be influenced by chlorides.

DR. H. SILVER: As Dr. Bechet pointed out, the patient is noncooperative, and I could not elicit a satisfactory answer with respect to a prior gonorrhea. The reason for my inquiry is that on closer examination I found hard, cornified, wax-colored nodules on the instep. These in association with the large, crusted, heaped up lesions which resemble bromoderma are part of the syndrome described by Vidal as keratoderma blennorrhagicum. There is no involvement of the joints

in this case, but clinically the lesions are more characteristic of keratoderma blennorrhagicum or psoriasis arthropatica than of bromoderma.

DR. H. KEIL (by invitation): Keratoderma blennorrhagicum is associated with painful involvement of the joints. The arthropathies are a constant part of the syndrome.

DR. P. GROSS: I should like to remove one of these crusts to see if there is an underlying dermatitis vegetans. The lesions do not impress me as being those of keratoderma blennorrhagicum. They are raised too much, and there is no positive history of gonorrhea or evidence of an involvement of the joints.

DR. A. ROSTENBERG: I do not think that the lesions resemble keratoderma blennorrhagicum. In this disease the eruption is more universal, and the lesions are smaller.

DR. H. SILVER: The hyperkeratosis on the soles and a few dry, scaly lesions on the arms would not fit into the clinical picture of bromoderma. After the crust is removed there appears a glistening surface which in addition to the aforementioned cornified lesions favors the diagnosis that I suggest. I do not make a positive diagnosis of keratoderma blennorrhagicum because the disorder is at a comparatively early stage. Further developments in the form of the appearance of new lesions or of the involvement of the joints will settle the diagnosis.

DR. F. CROSS: The patient is a man of clean habits; he says that he has never had gonorrhea. I regret that no examination of the prostate was made. It is most unusual to see keratoderma blennorrhagicum in a man of 70.

ANETODERMIA MACULOSA? Presented by DR. PAUL GROSS.

A Puerto Rican, aged 28, first noticed his cutaneous condition at the age of 15. It began on the forehead and spread to the neck, back, arms and the entire surface of the body. While the patient was living in Puerto Rico the condition was limited to the forehead and neck; it apparently became generalized in less than a year after he landed in the United States. He has been treated at Mount Sinai Hospital and the Polyclinic Hospital. The patient says that he has never had a venereal disease.

At the time of the examination there were numerous lentil-sized lesions on the trunk, presenting a cigaret paper-like atrophic surface. They were white, resembling depigmented spots, and in some places gave the impression of small morphea lesions. On the neck and the upper part of the chest and back were numerous irregularly shaped, grayish-brown spots which could be scraped off easily with the finger-nail.

The Wassermann test of the blood was negative. Urinalysis revealed only a slight trace of albumin. Repeated examinations of scrapings from the freckles gave negative results.

DISCUSSION

DR. L. DANTZIG (by invitation): The patient has had the condition since childhood. He noticed spots on the neck and chest at the age of 15. Later they spread to the rest of the body. We considered a diagnosis of mal de los pintos, but no fungi were found.

DR. S. PECK: The histology could not be made out, owing to the poor staining. The clinical picture as presented might well justify a diagnosis of anetodermia. Slides stained with ordinary methods did not throw light on this difficult case.

DR. S. FELDMAN: I suggest the use of polychrome orcein stain for the study of the elastic tissue.

DR. M. UMANSKY: The case is one of primary macular atrophy and closely resembles that of another patient who has recently been presented before this society. In typical cases, the primary lesion is usually a papule.

DR. H. SILVER: After a careful examination of the patient, I find that it is difficult to fit this case into the picture of Jadassohn's anetodermia. The clinical

manifestations of anetodermia maculosa of Jadassohn are varied. The case described originally by Jadassohn is a classic example of the disease and should serve as a pattern. Oppenheim differentiates three clinical stages. The first stage is characterized by the appearance of reddish macules or papules, and at this stage the disease offers difficulties in differential diagnosis, and mistakes are common. Even Jadassohn made the error of identifying a case, presented by Thibierge under the diagnosis of macular anetodermia, as one of anetodermia. It was subsequently proved to be a case of lupus erythematosus.

The macular or papular lesions are paler in the center and have a distinct ringed lesion. The appearance of these lesions marks, according to Oppenheim, the second stage. The final stage includes the typical round or oval, whitish, depressed or bullous-like lesions showing the phenomenon of herniation.

These features are absent in the case presented. The eruption is uniform, consisting of small, oval, whitish cigaret paper-like lesions. My impression is that we may be dealing with a guttate morphea.

DR. A. SAYER: I suggest that other diseases be considered: white-spot disease and lichen planus atrophicans.

DR. S. FELDMAN: Lichen planus atrophicans can be ruled out, for in it we should see all stages of lichen planus.

DR. D. BLOOM: Has the presenter considered poikiloderma atrophicans?

DR. P. GROSS: Achromia parasitaria can easily be ruled out. The condition may be morphea. After listening to Dr. Silver's discussion, I am beginning to doubt that it is anetodermia, unless it is one of unusual type.

PYODERMIA CHRONICA PAPILLARIS ET EXULCERANS. Presented by DR. PAUL GROSS.

The patient was previously presented before this society and the dermatologic section of the Academy of Medicine. He is shown again to demonstrate the result of treatment.

DISCUSSION

DR. P. GROSS: About five years ago this patient suffered an injury to the right leg which resulted in osteomyelitis. After several operations for osteomyelitis cutaneous lesions developed on the lateral surface of the leg and on the dorsum of the foot. The lesions were treated, but grew worse. The patient was then treated with baths and wet dressings of potassium permanganate; he got better. Every possible test was made; they all proved to be negative. It is interesting that a hemolytic Staphylococcus aureus like that we obtained from the wound was found two years before when the patient had osteomyelitis. The intradermal test with staphylotoxin gave a larger urticarial erythema (2 by 1¼ inches [5 by 3.1 cm.] in diameter), which lasted several days, while tests for Monilia and Trichophyton were negative. These cases are rather stubborn. Many cases of pyodermia which are reported are in healthy young people. The process attacks only one leg, as though that leg were sensitized to the particular germ.

The ulcerations and sinuses have healed completely; even the periostitis has greatly improved with the same treatment. The only remaining change is a mild, infectious eczematoid dermatitis which is responding promptly to antiseptic ointments.

DR. D. BLOOM: I wish to recall the two cases of pyodermia gangrenosa which are still under the observation of Dr. Abramowitz and myself. What Dr. Gross had to say about the treatment bears out my opinion that the main factor to be considered in these cases is the general condition of the patient and the raising of his general resistance. As soon as the general health is neglected, relapse in the cutaneous lesions may take place. In one of our cases we found that blood transfusions are of paramount value in promoting healing.

Book Reviews

Handbuch der Haut- und Geschlechtskrankheiten. Edited by J. Jadassohn. Volume 23. **Die Haut- und Geschlechtskrankheiten im Staats-, Straf-, Zivil- und Sozialrecht. Entwurf einer Geschichte der ansteckenden Geschlechtskrankheiten.** By J. Heller and G. Sticker. Price, 88 marks; bound, 96 marks. Pp. 642, with 37 illustrations. Berlin: Julius Springer, 1931.

In this volume two subjects are developed in a way to indicate the close relationship: first, cutaneous and venereal diseases in their legal, penal, civil and social relations, by Prof. Julius Heller of Berlin, and second, an outline of the history of contagious venereal diseases, by Prof. George Sticker of Würzburg. Two hundred and sixty-three pages are given to the first subject and 338 to the second. As is the case in the other contributions to this encyclopedia, the various topics included in these two subjects are handled in detail. One can hardly imagine any aspect which is not given consideration. THE ARCHIVES has had occasion repeatedly, in considering the other volumes, to comment on their completeness and accuracy and the excellency of their scholarship. This volume justifies the praise which has been given to the others and is another valuable unit in this great work.

Directory of Dermatologic Societies *

FOREIGN

British Association of Dermatology and Syphilology (Canadian Branch)

Alberic Marin, President, Drummond Medical Bldg., Montreal.
Antonio Sabetta, Secretary-Treasurer, 3435 St. Denis St., Montreal.
Place: Hamilton, Ontario. Time: 1934.

Royal Society of Medicine, Section of Dermatology

A. M. H. Gray, President, 30 New Cavendish St., W. 1, London.
W. N. Goldsmith, Secretary, 6, Upper Wimpole St., W. 1, London.

NATIONAL DERMATOLOGIC SOCIETIES

American Medical Association, Scientific Assembly, Section on Dermatology and Syphilology

C. Guy Lane, Chairman, 416 Marlboro St., Boston.
Harry R. Foerster, Secretary, 208 E. Wisconsin Ave., Milwaukee.
Place: Cleveland. Time: June 11-15, 1934.

American Dermatological Association

Harold N. Cole, President, 1422 Euclid Ave., Cleveland.
W. H. Guy, Secretary, 500 Penn Ave., Pittsburgh.
Place: New York. Time: June 7-9, 1934.

SECTIONAL DERMATOLOGIC SOCIETIES

Baltimore-Washington Dermatological Society

Harry F. Anderson, President, 1610, 20th St. N.W., Washington, D. C.
Joseph V. Kennedy, Secretary, 1835 Eye St., Washington, D. C.

Central States Dermatological Association

Joseph Brumberg, President, 528 Delaware Ave., Buffalo.
William F. Hoover, Secretary, 333 Linwood Ave., Buffalo.
Place: Buffalo. Time: 1934.

Iowa and Western Illinois Dermatological Association

J. C. Kessler, President, University Hospital, Iowa City.
Robert E. Jameson, Secretary, 1014 First National Bank Bldg., Davenport, Iowa.

New England Dermatological Society

Rudolph Jacoby, President, 270 Commonwealth Ave., Boston.
J. Harper Blaisdell, Secretary, 5 Bay State Road, Boston.
Place: Boston. Time: April 11, 1934.

Southern Medical Association, Section on Dermatology and Syphilology

Thomas W. Murrell, Chairman, 17 E. Grace St., Richmond, Va.
C. C. Dennie, Secretary, Professional Bldg., Kansas City, Mo.
Place: San Antonio, Texas. Time: November, 1934.

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* Secretaries of dermatologic societies are requested to furnish the information necessary for the editor to make this list complete and to keep it up to date.

STATE DERMATOLOGIC SOCIETIES

Florida Society of Dermatology and Syphilology

Chairman for each meeting is elected from city in which meeting is held.
Elmo D. French, Secretary, 602 Huntington Bldg., Miami.
Place: Jacksonville. Time: July 2, 1934.

Louisiana Dermatological Society

J. A. Devron, President, 150 Baronne St., New Orleans.
M. T. Van Studdiford, Secretary-Treasurer, 912 Pere Marquette Bldg., New Orleans.

Medical Society of the State of New York, Section on Dermatology and Syphilology

George M. Fisher, Chairman, 264 Genesee St., Utica.
Frank Combes, Secretary, 80 W. 40th St., New York.

Medical Society of the State of Pennsylvania, Section on Dermatology

Herbert J. Smith, President, 3303 N. 17th St., Philadelphia.
Robert L. Gilman, Secretary, 1930 Chestnut St., Philadelphia.

Michigan State Medical Society, Section on Dermatology and Syphilology

Robert C. Jamieson, Chairman, 1551 Woodward Ave., Detroit.
A. R. Woodburne, Secretary, Grand Rapids Clinic, Grand Rapids.
Place: Battle Creek. Time: September, 1934.

Minnesota Dermatological Society

D. D. Turnacliff, President, 407 Medical Arts Bldg., Minneapolis.
L. H. Winer, Secretary, 522 Medical Arts Bldg., Minneapolis.
Time: First Wednesday in October, December, February and April.

Oklahoma Dermatological Association

W. A. Showman, President, 108 W. 6th St., Tulsa.
C. L. Brundage, Secretary, 505 Osler Bldg., Oklahoma City.

Texas Dermatological Society

Everett C. Fox, President, 1719 Pacific Ave., Dallas.
Everett R. Seale, Secretary, 1215 Walker Ave., Houston.

LOCAL DERMATOLOGIC SOCIETIES

Atlanta Dermatological Society

Francis G. Jones, President, 384 Peachtree St., Atlanta, Ga.
Charles A. Wilkins, Secretary, Medical Arts Bldg., Atlanta, Ga.

Bronx Dermatological Society

Samuel Feldman, Chairman, 1955 Grand Concourse, New York.
Henry Silver, Secretary, 290 West End Ave., New York.

Brooklyn Dermatological Society

Arthur Persky, President, 1750 Ocean Parkway, Brooklyn.
George F. Price, Secretary, 884 Lincoln Place, Brooklyn.
Time: Third Monday of each month except June, July, August and September.

Buffalo-Rochester Dermatological Society

Earl D. Osborne, President, 471 Delaware Ave., Buffalo.
Richard L. Saunders, Secretary, 333 Linwood Ave., Buffalo.

Chicago Dermatological Society

Oliver S. Ormsby, President, 25 E. Washington St., Chicago.
Max Wien, Secretary, 104 S. Michigan Ave., Chicago.

Cincinnati Dermatological Society

Harry L. Claassen, President, Provident Bank Bldg., Cincinnati.
Raymond G. Senour, Secretary-Treasurer, 19 W. 7th St., Cincinnati.

Cleveland Dermatological Society

S. Littman, President, 10515 Carnegie Ave., Cleveland.
H. G. Miskjian, Secretary, 856 Rose Bldg., Cleveland.

Detroit Dermatological Society

H. L. Keim, President, 10 Witherell St., Detroit.
William G. Saunders, Secretary-Treasurer, 9203 Grand River Ave., Detroit.

Los Angeles Dermatological Society

Stanley O. Chambers, Chairman, 727 W. 7th St., Los Angeles.
Nelson P. Anderson, Secretary, 2007 Wilshire Blvd., Los Angeles.

Manhattan Dermatologic Society

Howard Fox, Chairman, 140 E. 54th St., New York.
Mihran B. Parounagian, Secretary, 126 E. 39th St., New York.

Montreal Dermatological Society

J. F. Burgess, President, Drummond Medical Bldg., Montreal, Canada.
B. Usher, Secretary-Treasurer, 1538 Sherbrooke St., W., Montreal, Canada.

New York Academy of Medicine, Section of Dermatology and Syphilis

Leo Spiegel, Chairman, 241 W. 100th St., New York.
Eugene F. Traub, Secretary, 140 E. 54th St., New York.

New York Dermatological Society

Edward R. Maloney, President, 853 7th Ave., New York.
R. H. Rulison, Secretary, 145 E. 54th St., New York.

Omaha Dermatological Society

Alfred Schalek, Chairman, 721 Medical Arts Bldg., Omaha.
Donald J. Wilson, Secretary, 1216 Medical Arts Bldg., Omaha.

Philadelphia Dermatological Society

Jacques P. Guequierre, Chairman, 1930 Chestnut St., Philadelphia.
Robert L. Gilman, Secretary, 1930 Chestnut St., Philadelphia.

Pittsburgh Dermatological Society

Frederick Amshel, Chairman, 3401 5th Ave., Pittsburgh.
Bernhard Goldmann, Secretary, Jenkin's Arcade, Pittsburgh.

St. Louis Dermatological Society

Richard S. Weiss, President, 3720 Washington Blvd., St. Louis.
M. F. Engman, Jr., Secretary-Treasurer, 3720 Washington Blvd., St. Louis.

San Francisco Dermatological Society

Ernest K. Stratton, President, 490 Post St., San Francisco.
John M. Graves, Secretary, 909 Hyde St., San Francisco.

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